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& GENERAL PRACTICE CLINICS

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FELIX MARTI-IBAÑEZ, M.D., Editor

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VOL. 169 NO. 2 WHOLE NUMBER 2876 FEBRUARY 1956

WALTER FINKE	Chronic Pulmonary Disease as a Possible Etiologic Factor in Lung Cancer	61
GEORGE J. BOINES AND STEVEN HOROSCHAK	Hesperidin and Ascorbic Acid in the Prevention of Upper Respiratory Infections	73
ERNEST JAWETZ	Fumagillin	77
	International Council on Health and Travel	83
	Editorial Survey: The Lung Cancer Puzzle	84
SELMAN A. WAKSMAN	Definition of "Antibiotic"	87

FOOD AND DRUG ADMINISTRATION ANNIVERSARY EDITORIALS

E. M. NELSON AND O. L. KLINE	Claims for Vitamins	89
FRANK A. VORHIES, JR.	Economic Cheats and the Law	91
ERNEST Q. KING	New Drugs	93
NEVIS E. COOK	The Why of Prescription Drugs	94
IRVIN KERLAN	Public Health Activities of the Food and Drug Administration	96
GORDON A. GRANGER	Therapeutic Devices and the Federal Food, Drug, and Cosmetic Act	98
GORDON A. GRANGER	Quackery and the Law	100
ALBERT H. HOLLAND, JR.	The Food and Drug Administration Physician	103

GENERAL PRACTICE CLINICS
Advanced Reports from Current Medical Meetings

L. KATZENSTEIN	Antibiotic Therapy of Bacterial Infections of the Skin	105
F. J. MURPHY AND N. P. GUADAGNI	The Use of a Steroid Anesthetic Agent	105
E. F. TRAUT AND E. W. PASSARELLI	A Study in Controlled Therapy of Degenerative Arthritis	106

GENERAL PRACTICE CLINICS *Continued*

G. W. Bethune — Advanced Mammary Cancer 107

E. W. Boland — Preliminary Clinical Experience with Metacortandracin in Rheumatoid Arthritis 108

J. J. Bunim — Arthritis in the Elderly Patient 109

M. Miller — The Use of Fructose in Treatment of Diabetic Acidosis 110

BOOK REVIEWS

Carl V. Weller — Causal Factors in Cancer of the Lung 111

Milton B. Rosenblatt and James B. Lisa et al — Cancer of the Lung. Pathology, Diagnosis and Treatment 111

Juan Torres Gost — Tratamiento de la Menigitis Tuberculosa y de la Tuberculosis Pulmonar Aguda 112

Arthur Osol and George E. Farrar, Jr., Editors — The Dispensatory of the United States of America 112

ANNOUNCEMENTS

Kalinga Prize Awarded to Dr. Augusto Pi-Suñer 114

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Chronic Pulmonary Disease as a Possible Etiologic Factor in Lung Cancer

Walter Finke, M.D., F.C.C.P.

ROCHESTER, N. Y.

The search for possible carcinogens in pulmonary cancer concentrates at present on extrinsic chemical agents that cause chronic irritation in the lower respiratory tract. Although it is generally recognized that in other organs certain types of chronic lesions can provoke malignant growth, the view that pre-existing pathologic changes may play a similar part in causing lung cancer now has few supporters. Nevertheless, investigations into the pathology of this condition, as well as certain clinical and statistical observations, do suggest that, in the lungs also, residue of previous diseases may be of etiologic significance.

Therefore, it was believed that a review of some previous observations on the association between chronic pulmonary disease and cancer, and an additional clinical investigation in this field, might be profitable.

PREVIOUS OBSERVATIONS

As early as in 1876, Friedlaender observed in the later stages of pneumonia in rabbits atypical proliferation of bronchial epithelium invading deeper structures.[1] Subsequently, this phenomenon, as a sequel to severe respiratory infections, was detected also in man.[2, 3] Metaplasia of bronchial epithelium, disorganized proliferation, and invasion of surrounding tissue were frequent findings in fatal influenza during the pandemic of 1918 to 1920, the histologic picture in these cases resembling an infiltrating malignant epithelial neoplasm.[4–9] This and the great number of bronchiectases and other lung-scarring conditions among surviving influenza victims led Winternitz and others to predict, some three decades ago, a possible future rise of lung cancer as a late result of that epidemic.

Experimental work in animals on lung tumors induced by chemicals has of late been supplemented by studies demonstrating that a combination of urethan with influenza virus causes a most extensive proliferation of bronchial epithelium.[10, 11] The tenacious although much disputed theory of viral or bacterial carcinogens seems

to be supported also by the histologic similarity between jagziekte, an infectious disease in sheep, and pulmonary adenomatosis in man.[12, 13]

Current comparative studies of human lung tissue have not confirmed a direct relationship between metaplasia and pulmonary cancer,[14–16] but pathologic proliferation of bronchial epithelium, especially of basal cells, continues to be considered important in the histogenesis of bronchogenic carcinoma.[2, 3, 11, 13–15, 17, 18] The phenomena of occult pulmonary cancer, of cancer in situ, and of malignant transformation of chronic bronchial inflammation may be subject to different interpretations; however histologic observations, such as those of the multicentric and peripheral origin of lung cancer in many instances and particularly Wittekind and Strueder's important studies in this field, suggest that chronic bronchitis may well be a "conditional" carcinogenic factor.[13–15, 17, 19–26] The difficulties in arriving at more definite conclusions stem chiefly from discordant opinions on what represents aberrative proliferation, innocent new growth, or true cancer.

Regardless of these and similar controversies, pulmonary tumors, including carcinomas, very often are found to arise at the site of or near old tuberculous, bronchiectatic, congenital, or other lesions. This would indicate that lung scars of various etiologies, rather than a particular one, may be responsible for the inception of new growths.[22, 23, 27–35] In Lueders and Themel's series, such scar cancers accounted for as much as 80 per cent of all peripheral malignant tumors of the lungs.[35]

With the exception of certain occupational diseases, no particular pulmonary affliction seems to predispose to lung cancer from a statistical point of view, although other types of antedating lung damage, such as warfare gassing, can be found in the history of patients with pulmonary cancer.[13, 17, 36, 37] Coincident tuberculosis has been noted in up to 10 per cent of lung cancer cases, but in pulmonary tuberculosis patients, coexistent cancer was observed in as few as 1 per cent or even less.[13, 17, 37–40] Long-standing chronic bronchitis, bronchiectasis, and chronic asthma have been reported in some 20 per cent of patients with pulmonary cancer,[37, 41–43] and the combined incidence of all previous chest ailments varies between one-third and two-thirds in investigated groups.[33, 37, 41, 43–44]

Doll and Hill found in patients with lung cancer, as well as in those with nonmalignant pulmonary disease, a significantly higher incidence of previous pneumonia and chronic bronchitis than in patients with gastric carcinoma.[42] They believed that these differences probably were due to the better recollection of previous respiratory disorders by patients with any type of chest ailments than by those with diseases in other systems. They admit as possible, however, a different interpretation of their data, namely, that chronic bronchitis and pneumonia may predispose to a whole group of respiratory diseases, including bronchial cancer.

Indeed, in a long-term follow-up study of life insurance holders with chronic bronchitis, there was not only an excessive mortality from pneumonia, influenza, asthma, and tuberculosis, but also the number of deaths from respiratory cancer was about five times the expected rate.[45] Another prospective investigation by Case and Lea[46] of persons with chronic bronchitis, in this case British veterans of World War I, also disclosed an excessive death rate from pulmonary carcinoma. Moreover, the results of this controlled study indicated that the chronic bronchitis,

rather than any particular cause of this condition, such as war gas, accounted for the high cancer rate.

It thus appears that previous chest disease may be important in the causation of lung cancer in man. Therefore, a study on the incidence of these ailments among patients with pulmonary cancer seemed to be warranted.

MATERIAL

The basic material for this investigation consisted of the hospital records of 159 unselected patients with primary pulmonary carcinoma, confirmed histologically by biopsy or autopsy and observed since 1940, the great majority of them after 1950. Forty-five of the records used were from the files of a cancer research institution,* 38 from the hospital of a medical school,† and 76 from a general hospital,‡ all in upstate New York. There were 139 men and 20 women patients; 21 cases of the whole group were less than 50 years of age when the cancer was diagnosed and 19 cases were aged 70 years or older.

The analysis of the records was not limited to the history taken routinely on admission but also included data from various diagnostic reports or other communications, and particularly the records of previous admissions for any reason. In order to establish the incidence of those respiratory manifestations and diseases that could reasonably be considered to have preceded the cancer, only those were included that had existed or occurred at least 10 years before the discovery of the cancer.

Accordingly, of the 159 cases, 41 per cent had a chronic cough; 17 per cent had influenza and/or pneumonia during the epidemic of 1918 to 1920; 19 per cent had pneumonia at some other time in their distant past; and, in 34 per cent, a chronic pulmonary disease of some type had been present. There was no appreciable difference between the incidence of chronic cough and chronic pulmonary disease among the cases of the three hospitals; that of influenza and pneumonia, however, was higher (38 and 25 per cent) in the first institution mentioned, where a detailed history questionnaire assured more accurate data on these illnesses.

Of the 55 patients with known long-standing chest ailments, 26 had had chronic bronchitis or bronchiectasis; 15, asthma; 12, suspected or confirmed pulmonary tuberculosis; and 2, silicosis. Most of those patients whose records indicated a chronic cough could be found in the category of chronic pulmonary disease and vice versa.

These figures were similar to those found in other investigations, but it appeared that in all probability the actual amount of previous respiratory sickness in this series had been much higher than was evident from the records. There were many cases with persistent cough of undetermined duration; in others, no adequate previous history had been taken because of the patient's poor condition on admission, language difficulties, or other reasons. Even more important, the patient's claim, at the time

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the cancer was found, of previous "excellent health" was frequently contradicted by older records. Therefore, it could not be expected that even the most meticulous search of the files, without additional sources of information, could furnish complete data.

Because no means were available for a retrospective investigation of all the 159 cases, a limited inquiry was attempted in about one half of this series, namely, 76 cases of the general hospital previously mentioned. Whenever possible, the desired information was obtained by personal interviews with the 13 patients still alive or with relatives of the deceased ones. Otherwise, a detailed questionnaire, individualized to the particular case, was sent to whoever might have had pertinent knowledge, including institutions in which the patient had been hospitalized in the past. Data of doubtful accuracy were checked with information from other sources, and previous respiratory illnesses were included in the tabulation only if their occurrence was established with reasonable certainty. Therefore, the data presented can be considered as conservative rather than maximum estimates (table I).

In 12 cases, the original records remained the sole source of information because relatives of the deceased could not be located or did not respond when contacted and no other source of information could be found. In 14 cases, some additional information as to the patient's previous respiratory health could be secured. In the remaining 50 cases, 7 of them women, the most complete information possible in such an inquiry was obtained, covering in most instances the patient's childhood also.

From the tabulation it appears that the incidence of chronic cough and known pulmonary disease increased in proportion to the completeness of the information; also, the incidence of epidemic influenza and of pneumonia proved to be far higher in the 50 cases with the most complete information.

Sixty per cent of the 50 most thoroughly re-investigated cases had had influenza in 1918 to 1920 or pneumonia before or after the epidemic, and an additional 18

TABLE I

Incidence of Chronic Cough, of Epidemic Influenza, and/or Pneumonia in 1918–1920, of Noninfluenzal Pneumonia, and of Chronic Pulmonary Diseases among 76 Patients with Lung Cancer, in Relation to the Completeness of the History Obtained

Type of group	No. cases	Chronic cough, per cent	Influenza and/or pneumonia, 1918 to 1920, per cent	Non-influenzal pneumonia, per cent	Chronic pulmonary diseases, per cent
Whole group: records only	76	40	8	20	28
No additional information available	12	40	0	14	33
Limited additional information obtained	14	65	7	14	50
Most complete additional information obtained	50	75	46	42	70

per cent had a history of particularly severe and protracted diphtheria, pertussis, bronchitis, or pleurisy. Forty per cent had been victims of the influenza epidemic and also of pneumonia at some other time or had been affected by multiple attacks of noninfluenzal pneumonia. In the majority of those patients who had had influenza at the end of World War I, this episode had been of serious character and complicated by pneumonia or early relapses. In this group of 50 patients with lung cancer, a definite chronic chest disease had existed in at least 70 per cent; an additional 14 per cent had been subject to recurrent and prolonged attacks of bronchitis, sinusitis, or other respiratory illnesses.

Thus, even though the group of 76 cases could be re-investigated only more or less completely, the incidence of chronic pulmonary disease rose from the original 28 per cent found in the records to 60 per cent when the supplementary data were considered. The distribution of various conditions among the 46 patients with chronic chest disorders was as follows: chronic bronchitis and bronchiectasis, 26; chronic asthma, 11; definite or suspected tuberculosis, 8; and silicosis, 1.

With the exception of the case of silicosis, some of those with tuberculosis, and 1 case of asthma initiated by war gassing, in patients with pre-existing chronic pulmonary ailments, the pattern of their history usually was very much the same. As a rule, a long-standing respiratory affliction could be traced back to childhood and had progressed in the course of years, requiring a great deal of medical care and excessive self-medication. Sulfonamides or antibiotics had been given once or repeatedly to at least half of these patients previously for acute respiratory illnesses and also for such conditions as postoperative complications and surgical infections. To many patients, their relatives, and the physicians, the episode that led to the detection of the cancer seemed at first merely another, more protracted one in the course of an old chest ailment complicated previously by pleurisy, pneumonia, lung abscess, asthma, or hemoptysis. The fact that most of these patients had not been in good respiratory health for a long time, even though their chest roentgenograms might have been "negative," in many instances appeared responsible for a delay in seeking medical advice for what turned out to be a cancer.

Quite often there was, however, roentgenologic evidence of some chronic respiratory condition at a time when a cancer could not be even suspected. In 28 of the 46 patients with previous respiratory ailments, old roentgenograms or reports on the findings could be located; in 11 instances, the oldest had been taken 5 to 10 years before the discovery of the lung cancer; in 10, from 10 to 20 years; and in 7, more than 20 years before this diagnosis was made. In 19 of these 28 old roentgenograms there was definite evidence of chronic pulmonary lesions, usually residuals of pleurisy and/or pneumonia, chronic bilateral emphysema, fibrosis, or calcifications suggestive of healed tuberculosis. In 6 additional cases, "increased markings" and "heavy hilus" were noted, findings generally interpreted as nondiagnostic but compatible with recurrent or chronic respiratory infection.

Roentgenograms taken from two to five years before the definite diagnosis of cancer were available in another 8 cases. In all of them, abnormal findings other than the suspicious lesion could have been due to secondary complications of a slow-

growing tumor but, if correlated to the patient's previous history, could have represented previous pathologic conditions as well.

Bilateral lesions were found in 16 of the 28 cases; in 3 others, the lesions were more pronounced in the lung that remained tumor-free later on. In only 8 instances did the new growth emerge on the side that seemed to have been the more diseased one. Even then, in only a few instances could one among several abnormalities be singled out that, in retrospect, could be reasonably considered as the cancer in its "silent phase."

In 9 cases, clubbing of the fingers or emphysematous chest deformities could be traced back to at least five years before discovery of the cancer. In 10 of those patients whose antedating respiratory disease could be demonstrated roentgenologically, the pathologic findings confirmed the existence of the old lesions.

Occult or minute cancers were reported in 7 autopsy cases. In 4 instances, the histologically malignant growth was found in or near residuals of previous lesions. In the 3 other cases, bilateral chronic emphysema, multiple healed tuberculous foci with chronic bronchitis, or residuals of empyema in the tumor-free lung were noted. Four of these 7 early cancers were found in women.

Some 75 per cent of the 50 patients, 43 of them men and 7 women, whose life histories could be re-investigated most completely, had smoked regularly at least one pack of cigarettes a day for many years; the remaining 25 per cent had been nonsmokers, had smoked less than one pack of cigarettes a day, or had been cigar and pipe smokers. As stated before, approximately 70 per cent of these 50 patients with lung cancer had been affected by a chronic chest disease of 10 or more years' duration. There were 22 cases of chronic bronchitis, 8 of chronic asthma, 5 of proved or suspected tuberculosis, and 1 of silicosis. Among 15 of the heaviest cigarette smokers with epidermoid lung cancer, 9 had had epidemic influenza at the end of World War I and 7 of these 9 also had had pneumonia at some other time, 10 or more years before their cancer was discovered.

A brother of the patient with silicosis and a brother of one of those with chronic bronchitis also had been victims of lung cancer. All 4 of these patients were heavy cigarette smokers, but both the first patient and his sibling had silicosis and the two other brothers had epidemic influenza after World War I.

For comparison with the cancer group, 43 men and 7 women patients hospitalized within a two week period, for various conditions, in the same institution in which the cancer patients had been admitted, were investigated as to their smoking habits and the incidence of chronic respiratory diseases. The ages of these patients corresponded closely to the ages that the patients with lung cancer had reached or would have reached if they had been alive at the time of this retrospective control study. Forty-eight per cent of this group had smoked at least one pack of cigarettes a day for many years; the remaining 52 per cent had been nonsmokers, had smoked less than one pack a day, or were cigar and pipe smokers. Twenty-four per cent of these control cases, which incidentally included 4 patients with some lung condition as the primary admission diagnosis, had a past history and evidence of a chronic chest ailment. There were 9 cases of chronic bronchitis, 2 of chronic asthma, and 1 of apparently old tuberculosis. Among these 12 patients with long-standing pulmonary

TABLE II

Incidence of Epidemic Influenza in 1918 to 1920, of Noninfluenzal Pneumonia, and of Multiple Attacks of These Illnesses in the Past of Patients with Lung Cancer, in Patients Hospitalized for Various Conditions, in Working Persons, and in Ambulatory Patients with Bronchopulmonary Disease

Group	No. cases	Influenza, 1918 to 1920, per cent	Noninfluenzal pneumonia, per cent	Multiple attacks, per cent
Lung cancer	50	46	42	40
Hospitalized	50	24	18	5
Working	136	26	14	4
Bronchopulmonary disease, ambulatory	271	48	42	21

disorders, 8 were heavy or excessive cigarette smokers; 2, moderate cigarette smokers; and 2, nonsmokers. Four of the 12 cases had had pneumonia at some time in their lives previous to the past 10 years, 2 had epidemic influenza in 1918 to 1920, and 1 was gassed during World War I.

Thus, there was a higher percentage of heavy or excessive cigarette smokers in the cancer group than in the controls. A similar difference also existed, however, between the incidence of long-standing pulmonary diseases, as well as previous attacks of influenza and pneumonia, in these two series (table II). Even more important, the incidence of multiple severe respiratory illnesses, either influenza and noninfluenzal pneumonia or more than one attack of pneumonia, was, in the control group, only one eighth of that in the group with pulmonary cancer. A similarly low incidence of these lung-damaging episodes, single and multiple, also was observed in the past history of another thoroughly questioned control group consisting of 117 men and 19 women working persons, 50 years of age and older (table II).

On the other hand, in a series of 178 men and 93 women ambulatory patients of the same age group with bronchopulmonary disease, 173 chronic bronchitis and 98 chronic asthma, the obtained figures on influenza and pneumonia proved almost identical to those in the cancer group. The only real difference between these two series as to their previous respiratory health was that the rate of repeated severe lung infections in the cancer group was twice that in the group of nonmalignant chest ailments (table II).

It should be mentioned that, according to morbidity statistics including areas of upstate New York, some 15 per cent of the older population is affected by tuberculosis, chronic bronchitis, bronchiectasis, or asthma.[47, 48] This figure is 9 per cent lower than that in the 50 cases hospitalized for various conditions but is only one fourth of that in the 76 cases of lung cancer hospitalized in the same institution.

DISCUSSION

As is becoming evident, lung cancer will be conquered by the elimination of its precipitating factors rather than by further improvement of diagnostic and surgical procedures. Therefore, all possible contributing causes of this disease, however

remote they may appear, should be investigated with an open mind. At present, more biologic and clinical evidence seems to point toward chronic pulmonary infection, with its sequelae, as one of the "nearer causes" of lung cancer than toward common inhaled chemical irritants in the absence of such an infection. Investigations into the etiology of pulmonary cancer necessarily remain incomplete if they fail to consider fully this important factor of previous infection and may even lead to erroneous conclusions.

The significance of acute, lung-damaging episodes in the distant past of patients with lung cancer, be they wounds, war gas poisoning, tuberculosis, pneumonia, or influenza, lies in the fact that they often initiate profound chronic processes. It is conceivable that the risk of malignant transformation increases with the frequency of pulmonary insults, including severe exacerbations of chronic disease, which produce repeated tissue unrest and disorganized reparative proliferation.

Bronchitis, asthma, bronchiectasis, or abscess may be complications of a slow-growing neoplasm, but this sequence of events is not likely if such disorders antedate the appearance of the cancer by many years or even decades. Similarly, uncharacteristic roentgenologic abnormalities preceding symptoms of a new growth may be an early sign of cancer;[38, 49] however, if such findings have been evident for 10 or 20 years in a patient with a known pulmonary ailment, it is more logical to interpret them as due to old, nonmalignant lung disease, as would be done in the case of tuberculous scars. Moreover, the so-called preclinical phase of a cancer very often is not a "silent" one, a persistent cough or other respiratory symptoms of many months' or years' duration being a frequent feature.[38, 49]

Little is added to our knowledge of the natural history of lung cancer by discounting such a chronic cough as "cigarette cough" or by accepting it as an almost universal, and therefore insignificant, phenomenon.[49–51] Cough, if persistent, almost always signifies bronchial disease. It is possible that chronic irritation from excessive smoking may render the respiratory system more vulnerable to respiratory infections, but this habit, like inclement weather, fumes, and smog, more often aggravates than causes bronchitis.[52] This condition reportedly occurs in only some 10 per cent of adults,[47, 48] far less than the number of smoking persons. In fact, indulgence in this habit may be induced by chronic bronchitis rather than vice versa. Irritation from smoking often facilitates expectoration, thus changing the "dry," most distressing, cough of patients with bronchitis and chronic asthma to a productive, more relieving, one. This, and the high nervous tension of sufferers from those ailments, drives many of them to heavy smoking as another type of self-medication.

At present, the rise in lung cancer is being related to various elements that entered the picture some 30 years ago. In addition to the increase in tobacco consumption and industry-caused factors, even the mounting circulation of newspapers and other printed material has been associated with the upward trend of pulmonary cancer.[51, 53–55] Important as these investigations are, in seeking a still hidden, additional cause for what is now called an epidemic of lung cancer, one cannot overlook the influenza pandemic of 1918 to 1920. Undoubtedly, that event burdened the respiratory health of many of its survivors with a severe, lung-damaging illness. In

most countries, it increased sharply the number of victims of chronic bronchitis, bronchiectasis, and asthma who would suffer multiple pulmonary illnesses before reaching old age.

From a statistical point of view, a possible causal relationship between that influenza pandemic and the subsequent rise in lung cancer has not yet been evaluated adequately. The small increase of this disease in Iceland in spite of a severe influenza epidemic at the end of World War I[56] does not in itself disprove the "influenza theory" of bronchogenic carcinoma. In Iceland, there was a particularly high mortality from influenza during the epidemic[57] and, in following years, the death rate from pneumonia exceeded by far that in England and the United States.[58] Thus, in Iceland, fewer persons survived as potential victims of lung cancer.

There is little doubt that the upward trend of this disease is due partly to the downward trend in deaths from tuberculosis, pneumonia, and other respiratory illnesses.[53] Moreover, it was the patient with chronic bronchopulmonary disease who, before the antibiotic era, was most likely to succumb to an acute exacerbation of his ailment. His average life span, like that of the tuberculous patient, now has been extended and usually is terminated by other causes, including lung cancer.

Because the incidence of acute respiratory illnesses is approximately the same in both sexes, the predominance of lung cancer in men is an important argument against the causal relationship between pre-existing chest diseases and pulmonary cancer. It is possible, however, that chronic pulmonary afflictions, like other chronic ailments, are commoner in men than in women. Of the 271 patients, older than 50, with chronic bronchitis, bronchiectasis, and infectious asthma (table II), for example, only one third were women. On the other hand, not only in this study, but also in others, a high percentage of the occult or minute lung cancers were found in women. Observations of this type suggest that certain factors related in some way to the sex, such as smoking, occupational irritants, and hormonal processes, may precipitate the activation of a dormant malignant growth.

Although the number of pre-existing chest ailments concentrated in the group of this study is impressive, it is admitted that, from a statistical point of view, the figures presented are open to various interpretations. However, this is the case even with regard to elaborate epidemiologic investigations, including the previously mentioned study of Doll and Hill[42] and the one by Hammond and Horn[54] on smoking and lung cancer, conclusive as they may appear.[59] Definite conclusions as to the cause of pulmonary cancer probably will be reached by further clinical, pathologic, and experimental observations, rather than by statistical methods alone. Nevertheless, the high incidence of previous respiratory sickness in retrospective investigations of patients with lung cancer and the increased death rate from respiratory cancer in prospective studies of persons with chronic bronchitis[45, 46] corroborate, and certainly do not contradict, the thesis of an etiologic relationship between nonmalignant and malignant chest ailments. If further work on this problem proves the factor of pre-existing disease to be of significant magnitude, it could be hoped that by controlling and, even more, preventing, this precursor, one contributory cause of bronchogenic carcinoma can be eliminated.

The importance of preventing common chronic chest diseases does not depend entirely, however, on whether or not they predispose materially to malignant growth. Eradication of tuberculosis by prompt and adequate treatment of the initial lesion now seems possible in the foreseeable future and is striven for vigorously. Equally important is the control of suppurative bronchopulmonary diseases, such as chronic bronchitis, bronchiectasis, and infectious asthma by immediate and, if necessary, prolonged antibacterial therapy at their onset.[60-62, 64, 65] Since familial contagion appears a major factor in the spread of these respiratory conditions, adequate protection of children from contacts is even more rational.[60]

While thousands of lives are now saved by even short antibiotic treatment of pneumonia and similar illnesses, an ever-increasing number of apparently recovered patients become potential pulmonary cripples because of insufficient therapy.[60-62] Ridding the population of chest diseases, including cancer, now is hoped for by eliminating the irritant effect of atmospheric pollution, dust, fumes, and smoking. The prospects for improving the respiratory health of man would be brighter if at the same time damage from infection were prevented or minimized. The mere possibility that one sequela to severe respiratory infection, with or without additional factors, may be lung cancer, makes prophylactic efforts even more imperative. If the present study does no more than to stimulate further thought and observation on this problem, it will have served its purpose.

SUMMARY

Certain pathologic and clinical observations have suggested that chronic pulmonary disease may be one among other precipitating factors in lung cancer. Two recent follow-up surveys of persons with chronic bronchitis indicate an increased risk of respiratory cancer in this group.

An analysis of the hospital records of 159 patients with proved primary lung cancer revealed that, in one third of these cases, a long-standing pulmonary ailment had existed. This figure rose to 60 per cent in those 76 of the 159 patients whose records could be supplemented by additional information and reached at least 70 per cent in the 50 most completely re-investigated cases. The commonest preexisting chest ailments were chronic bronchitis and asthma, although old tuberculosis accounted for a substantial number of cases. The incidence of these respiratory disorders proved far higher in the cancer group than in two control groups and in the general population of cancer age.

The incidence of epidemic influenza in 1918 to 1920 and of pneumonia in the patient's distant past was particularly high in the cancer group but was practically identical with that in patients with bronchopulmonary disease. However, in this latter group, the rate of multiple lung-damaging episodes was only half that found in the series of 50 cases of pulmonary cancer.

The results of this study support the view that chronic pulmonary disease may be one of the "nearer causes" of bronchogenic carcinoma. Although more extensive research is needed to evaluate the actual magnitude of this factor, control and, even more, prevention of these conditions are, in themselves, important goals.

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Hesperidin and Ascorbic Acid in the Prevention of Upper Respiratory Infections

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This study stems from observations made on a number of poliomyelitis patients treated with hesperidin and ascorbic acid (Hesper-C‡) five years ago as a prophylactic measure to maintain normal capillary integrity. We originally treated 48 patients, ranging in age from 15 to 35 years, with 800 mg. each of hesperidin and ascorbic acid daily, to correct capillary fragility, and then continued these patients on 200 mg. of each substance as a prophylactic measure to maintain normal capillary integrity.

At the end of the winter months, a number of these patients inquired if the pills "prevented colds." They found that they had been free of colds, while members of their families had to be treated for colds. These reports aroused our interest and stimulated us to survey all 48 patients given hesperidin and ascorbic acid in order to maintain normal capillary integrity, but without intending to prevent the common cold.

Our first survey disclosed the following data: (1) 48 patients were started on hesperidin and ascorbic acid; (2) of these, 40 reported no colds or experienced only one or two mild attacks; (3) the remaining 8 said their colds were as bad as or worse than those of the previous winter; and (4) 35 family contacts of these patients sought medical advice and attention from their physicians on an average of three times during this period.

It was decided to follow these patients for another year to observe what effect hesperidin and ascorbic acid would have on the incidence of colds in these same patients. They were advised to continue with the capsules of hesperidin and ascorbic acid (100 mg. of each substance per capsule), two capsules daily, throughout the year.

Following the second winter season, we obtained reports from 42 of the 48 patients, as follows: (1) of the 42 patients, 37 were adequately "protected," since they reported no colds or one to two mild colds; (2) 4 patients each reported three colds, lasting an average of three days in each instance; (3) 1 patient reported five colds, each lasting five to seven days; and (4) family contacts not taking hesperidin and ascorbic acid sought relief for colds on an average of three times during this period.

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‡ The trade name of the Medical Research Department, National Drug Co., for a capsule containing 100 mg. each of hesperidin and ascorbic acid is Hesper-C. Hesperidin was originally administered in a tablet containing 50 mg. of each of hesperidin and ascorbic acid. The hesperidin and ascorbic acid used in this study were supplied through the courtesy of the Medical Research Department, National Drug Co., Philadelphia, Pa.

The data obtained in our second survey are intriguing; however, we cannot argue with the reports given by the patients. We appreciate the variable incidence of upper respiratory infections from year to year and the fluctuation of resistance to infection. It was decided to set up a controlled study in this series of patients.

For the third year, the 37 patients were divided into group I and group II. Group I was represented by 18 patients who had apparently been "protected" against the common cold while taking hesperidin and ascorbic acid for the previous two years. These patients were advised to discontinue the capsules of hesperidin and ascorbic acid and to take orange juice three times daily. This was our control group.

Group II consisted of 19 patients, including the 5 patients who reported colds during the last survey. They were continued on 200 mg. of hesperidin and ascorbic acid daily.

A review of the information obtained from these patients revealed the following: in group I, (1) 10 reported no colds or one to two mild attacks; and (2) 8 had two or more colds requiring medical attention. We did not prescribe any hesperidin and ascorbic acid in these cases because we were using the combination as a prophylactic and not as a therapeutic agent.

In group II (1) 15 patients reported no colds or one to two mild attacks of an average of two days; and (2) 4 patients reported three to five colds, but none severe enough to call a doctor.

This survey indicates that the combination of hesperidin and ascorbic acid is apparently able to "protect" against the common cold. In order to substantiate this finding, it was decided to reverse the two groups observed during the third year.

For the fourth year, we established these two groups: group I, represented by the 18 patients used as controls in the third year were placed on 200 mg. of hesperidin and ascorbic acid daily and group II, represented by 19 patients in whom dosage of hesperidin and ascorbic acid was substituted for orange juice, were now the control group.

A follow-up survey of these two groups resulted in the following data: in group I, (1) 13 reported no colds or one to two mild colds; (2) 1 reported three colds and another, five colds of three days' duration; and (3) 3 patients gave no report.

Group II, (1) 9 reported no colds or only several mild attacks; (2) 8 patients reported two to three attacks of three to five days' duration; and (3) 2 patients did not report.

We have made it a routine practice to place all of our poliomyelitis patients on hesperidin and ascorbic acid, starting in the hospital as a therapeutic measure to correct abnormal capillary resistance and then in outpatients as a prophylactic measure to maintain normal capillary integrity. The aforementioned trend seems to prevail in a vast majority of patients.

DISCUSSION

A clearer understanding of the importance of the capillary system and its physiologic function will convince even the skeptic that "an intact capillary system means a solvent body."[1] The capillary system, among its other functions, acts as "a pro-

tective mechanism against disease."[2] Whether in health or in disease, the capillary system is an important factor.

Impaired nutrition and infection contribute to injury of the capillary walls.[3] The barrier function of the endothelial cells may be impaired by various factors, but, we believe, particularly by a deficiency in protein and certain vitamins. Depletion of ascorbic acid contributes to lowered body resistance to infection.[4] We have pointed out that in poliomyelitis patients, the infection creates a tissue deficiency,[5] and, we now add, a tissue deficiency predisposes to infection.

Capillary resistance depends on the adequate formation and maintenance of intercellular ground substance. According to Youmans,[6] "The primary structural change in vitamin C deficiency is a disturbance in the formation and maintenance of the intercellular ground substance. Apparently ascorbic acid is essential for the integrity of this tissue. In the intercellular ground substance are the collagen bundles. In the absence of a sufficient supply of ascorbic acid, the collagen bundles disappear and the ground substance takes on a thin 'watery' appearance and may eventually disappear." The nature of the dietary factors contributing to the maintenance of vascular integrity has not been unequivocally elucidated. Wolbach[7] stated that vitamin C seems to play a specific role by functioning in some manner to incorporate the vascular cement substance.

Bronte-Stewart[8] emphasized that "ascorbic acid by itself has no proved effect in combating any condition other than scurvy." According to Scarborough,[9] a deficiency of vitamin C is not necessarily complicated by low capillary resistance. Warter et al[10] confirmed reports that there is no correlation between capillary fragility, as measured by various methods, and plasma vitamin C levels.

A substance of similar importance and related activity was postulated[11] to accompany cellular vitamin C. This substance was isolated from citrus fruits and extracts of Hungarian red pepper and was labeled "citrin,"[12] which on analysis was found to be a mixture of hesperidin and eriodictin.[13]

The permeability activity of hesperidin was studied by Scarborough,[14,15] who found that this substance increased capillary resistance in man when given by mouth.

A synergism of vitamin C and vitamin P is suggested by some studies.[16] Warter et al[10] suggested that hesperidin is essential for the absorption and retention of vitamin C, acting synergistically in maintaining normal capillary resistance. The demonstration of a relationship between hesperidin and ascorbic acid by Beiler and Martin[17] shed some light on the basic mechanism involved. Selsman and Horoschak[18] suggested, on the basis of their experiences, that the presence of hesperidin is necessary in the utilization of vitamin C for the intercellular substance.

There is sufficient evidence to support this concept that the full activity of vitamin C depends on the presence of hesperidin for the formation and maintenance of the intercellular cement substance.

COMMENT

Our primary reason for using the combination of hesperidin and ascorbic acid was and continues to be to improve and maintain capillary resistance in poliomyelitis

patients and not to determine how effectively the product influences resistance to upper respiratory infection. It is our firm conviction that a pathologic condition of the capillary system is one of the underlying factors in many acute and chronic ailments. Reversal from abnormal to normal capillary resistance is essential for good therapeutic results. There is adequate clinical evidence that the hesperidin and ascorbic acid is an effective agent for this purpose.

We appreciate the variability of seasonal incidences and severity of upper respiratory infections. The above data are presented as observations based on our poliomyelitis therapeutic program, which may have some definite significance. These data are not offered as clinical conclusions that establish the prophylactic capacities of hesperidin and ascorbic acid against the common cold. However, we do believe the results suggest that a large-scale study is justified.

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Fumagillin

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In 1949, Hanson and Eble[1] described how, from a species of *Aspergillus* numbered H-3, they isolated an agent capable of inhibiting bacteriophage for *Staphylococcus aureus* 209. Eble and Hanson[2] found that their species of *Aspergillus* was similar to but not identical with *Aspergillus fumigatus* NRRL 171 and therefore they named the agent fumagillin.* Phagopedin sigma, a bacteriophage-inhibiting agent isolated by Asheshov et al,[3] was shown to be identical with fumagillin. This substance had only low antibacterial activity and did not affect animal viruses, such as those of poliomyelitis or influenza, in vivo. That this substance might have valuable antiamebic properties was first discovered by McCowen et al[4] in 1951, and its use in human medicine has been virtually limited to the treatment of amebiasis since then.

The original production method[1] involved growing the *Aspergillus* in dextrin corn steep medium in shake flasks, extracting the liquor with chloroform, and drying the brownish yellow gum that precipitated. Four hundred fold purification could be obtained by repeated extraction of the crude material with various organic solvents (ethers, methanol, cyclohexane) in which the active principle was readily soluble. Present production methods[5] involve the inoculation of soybean steep liquor medium in large-scale fermenters with a suitable antibiotic-producing strain of *A. fumigatus*, incubation with vigorous agitation and aeration for three to five days, and removal of the mycelium by filtration. The filtrate is adjusted to an acid *p*H with sulfuric acid and the antibiotic extracted with organic solvents. After clarification, the solvent is evaporated to a small volume, at which point the fumagillin crystallizes out. The crystals are washed, recrystallized, and dried in vacuo.

The crystalline form of the antibiotic isolated by Eble and Hanson[2] was found to contain carbon, hydrogen, and oxygen only. The substance was a weak acid, soluble in most organic solvents and dilute alkali, but insoluble in saturated hydrocarbons, water, and dilute acid. The tentative empirical formula was $C_{27}H_{36}O_7$. The ultraviolet absorption spectrum showed peaks at 335 and 351 mμ and a minimum at 240 mμ. Schenck et al[6] hydrolyzed fumagillin under mild alkaline conditions, liberating a highly unsaturated acid, $C_{10}H_{10}O_4$, with the properties of 2,4,6,8, decatetraenedioic acid. Hydrolysis of hydrogenated fumagillin yielded sebacic acid. They concluded that fumagillin is a mono-ester of decatetraenedioic acid and an alcohol $C_{16}H_{28}O_4$ and suggested the structure $[C_{16-17}H_{25-27}O_3]$—O—CO—$(CH=CH)_4$—COOH. Biologically and chemically, fumagillin is distinct from fumigacin, fumigatin, helvolic acid, gliotoxin, and spinulosin, all of which have been isolated from various strains of *A. fumigatus*.

Fumagillin is destroyed by exposure to air and light[7] or heat under anaerobic conditions.

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* The trade name of the Abbott Laboratories for fumagillin is Fumidil.

ANTIMICROBIAL ACTIVITY

In the initial work of Hanson and Eble[1] it was pointed out that the bacteriophage-inhibiting activity of fumagillin is high but the antibacterial or antifungal activity low. A number of common gram-positive bacteria were inhibited by concentrations of 30 to 300 μg./ml., but most of the gram-negative bacteria were quite resistant to 300 μg./ml. Fungal pathogens were likewise not inhibited by 100 μg./ml. in an agar dilution test.

McCowen et al[4] indicated that a dilution of 1:131,062,000 of crystalline fumagillin in vitro inhibited the growth of *Endamoeba histolytica* (strain NIH200) in cultures also containing a mixed bacterial flora. It was emphasized that bacteria were not inhibited and that therefore the drug acted directly on the amebae rather than on the bacteria on which the amebae feed.

Hrenoff and Nakamura[8] likewise found an in vitro effect of fumagillin against *E. histolytica* in concentrations of 1:10,000,000 to 1:15,000,000. The action appeared to be amebicidal rather than merely inhibitory. Balamuth[9] also stressed the direct amebicidal effect. In vitro exposure of cysts of *E. histolytica* to fumagillin in a dilution of 1:2,000,000 to 5,000,000 is sufficient to destroy them in less than one hour.

Experiments in patients indicate that other protozoa also are inhibited. Killough et al[10] found that, in patients treated with 5 to 50 mg. of fumagillin a day, *Endamoeba coli*, *Giardia lamblia*, *Cheilomastix mesnili*, *Endolimax nana*, and *Iodameba buetschlii* promptly disappeared from the stools but recurred after discontinuance of the drug. On the other hand, *Plasmodium*, *Schistosoma*, *Ascaris*, hookworms, and other helminths were not affected.

The combined effect of fumagillin and other antiamebic drugs was studied by Nakamura et al[11] in naturally infected macaque monkeys. Neither fumagillin nor oxytetracycline administered singly, in doses of 50 mg./day for 10 days, cleared these animals of *E. histolytica* infection. However, when the two drugs were given together, 12.5 mg. of each for 10 days, 4 out of 5 monkeys were permanently cleared of infection. This apparently synergistic effect was further studied in vitro by observing the inhibition of respiratory activity of amebae by various drugs singly and in combination. Statistical evaluation of the results indicated that fumagillin was synergistic with thiocarbarsone or oxytetracycline, but only additive with emetine or chlortetracycline.

The causative agent of nosema disease of bees was inhibited by fumagillin and its salts, including the bicyclohexylammonium salt.[25]

PHARMACOLOGY

The initial crude preparations of fumagillin were relatively toxic. The LD_{50} for mice was 9.6 mg. injected subcutaneously. Later, crystalline preparations had a much lower acute toxicity so that the LD_{50} for mice was approximately 800 mg./Kg. injected subcutaneously.[12] There was marked species variability in toxicity tests on animals. Whereas rats tolerated oral doses in excess of 50 mg./Kg./day for more than two weeks, dogs or cats often died in that time after daily doses of only 5 mg./Kg./day. Characteristic toxic effects in animals were anorexia, vomiting,

diarrhea, intestinal hemorrhage, and weight loss. Most of these symptoms and signs were probably attributable to direct irritant effects on the mucous membranes of the intestinal tract. At higher dosage levels, damage to renal tubules and liver function (depressed prothrombin activity) have occurred in dogs and cats.

With ordinary doses in man, absorption of low doses from the intestinal tract appears to be negligible and, as a consequence, allergic manifestations and significant systemic toxic effects have not been observed. In carefully observed patients who received 50 to 100 mg. of fumagillin in 10 to 12 days, Anderson et al[13] were unable to detect any effect on the blood-forming organs, liver or kidney function, or electrocardiogram. McHardy et al[14] conducted a tolerance trial in 10 normal persons, starting at doses of 10 mg./day of fumagillin and increasing the dose by 10 mg. increments to 100 mg./day. At levels of 10 to 20 mg./day, no side effects were seen. At 30 to 50 mg./day, all subjects experienced anorexia and some had nausea and abdominal discomfort. At 60 mg./day or more, all subjects had malaise, nausea, distention, abdominal discomfort, and vertigo, and a few developed diarrhea and superficial desquamation of the skin of the hands and feet. On the other hand, Black et al[15] concluded, on the basis of abnormal thymol turbidity and zinc sulfate flocculation tests, that "fumagillin has an adverse effect on liver function in certain patients." They also observed poor ability to concentrate urine in 11 of 27 patients receiving fumagillin and concluded that the drug may depress renal tubular function in some patients. Occasionally one of the patients developed a skin rash.

In a group of 22 patients receiving 50 mg./day of fumagillin in gelatin capsules, Killough et al[10] found only 2 instances of dizziness and 4 of anorexia. In contrast, 3 patients whom Schindel[16] treated with 500 to 570 mg. of fumagillin in more than 10 days developed anorexia, nausea, gastrointestinal upsets, peeling of the palms and soles, headaches, and hearing difficulties, all of which eventually disappeared. Hernandez de la Portilla et al[17] found the same side effects in 7 patients treated with fumagillin in doses of 50 to 200 mg./day for 9 to 14 days, and also described urticaria in 3 of them. However, they found no abnormalities in laboratory tests designed to measure renal, hepatic, or bone marrow function.

On the basis of the evidence summarized, it can be concluded that, in doses less than 40 to 50 mg./day, there is probably little absorption of fumagillin from the intestinal tract and usually no systemic toxicity. At higher doses, there must be some absorption and distribution of the drug to account for the side effects that have been observed. With oral doses of 10 to 20 mg./day, it can be expected that only a few individuals will develop anorexia and nausea, and all side effects observed with doses less than 40 mg./day are probably largely attributable to local irritation of the intestinal tract by the drug. Except for rare instances of leukopenia, there are, to date, no reported data on depression of hematopoietic function by therapeutic doses of fumagillin.

DOSAGE FORMS

Fumagillin is manufactured presently by only one pharmaceutical house in the United States, and is distributed in sugar-coated tablets containing 10 mg. of crystalline drug. Because of the well-known instability of fumagillin, a special formulation

has been developed to stabilize the product to insure adequate shelf life without decomposition from light, heat, or air.

The recommended initial dose is 10 mg. of fumagillin three times daily. If this dose is tolerated well, it may be raised by daily increments of 10 mg. up to a maximum total dose of 50 to 60 mg./day. Administration should continue for 10 to 14 days. If the *E. histolytica* infection relapses, a second course of drug of similar dose and duration may be administered. The manufacturer of fumagillin proposes that children receive proportionately smaller doses, calculated on the basis of the patient's weight and age. The dose should probably not exceed 1 mg./Kg./day. The only significant series of children treated with this drug was reported by Anderson et al.[18]

For the treatment of nosema disease in bees, a mixture of bicyclohexylammonium fumagillin, various buffers, and sugar is made into a sirup that is fed to bees in an optimal concentration of 75 to 100 mg. of fumagillin activity per gallon of sirup. This treatment is said to promote colony growth and increase honey production.[25]

CLINICAL USE

In medical therapy, fumagillin has only a single indication: the treatment of *E. histolytica* infection, either as acute amebic dysentery or in the chronic carrier stage. Since ordinary recommended doses of fumagillin taken orally are not significantly absorbed, only intestinal amebiasis can be effectively treated. Amebic abscesses in other tissues and amebic hepatitis are not significantly influenced. Intestinal bacteria are not suppressed to any extent, and fumagillin has no effect on bacillary dysentery.

Killough et al[10] treated 22 patients with *E. histolytica* infection with fumagillin in doses ranging from 5 to 50 mg./day for 7 to 14 days. Twelve of these patients were asymptomatic, 9 had symptoms of mild gastrointestinal disturbance, and 1 had severe amebic dysentery. In the stools of the asymptomatic and mildly symptomatic patients, the parasites disappeared promptly, within 48 hours, but the patient with severe dysentery did not respond. During the follow-up period of two months, the majority of patients remained free from infestation and only in 3 persons (treated with 5 to 10 mg./day) did the parasites reappear. Other intestinal protozoa also disappeared during this therapy but recurred irregularly later.

Anderson et al[12] found that 9 of 10 asymptomatic cyst passers were cleared of *E. histolytica* by 100 mg. of fumagillin administered over a period of 12 days. A total dose of 50 mg. given over the same period cleared only 4 of 10 cyst passers.

McHardy[19] studied 175 patients with all types of amebic infection. Of this group, 86 patients received 60 mg./day of fumagillin for 10 days, 28 patients received 40 mg./day for 10 days, and 61 patients were treated with 20 to 30 mg./day for shorter periods. The over-all therapeutic efficacy (i.e., stools free from amebae) was 93.7 per cent in those who could be adequately followed, but, in 41.1 per cent of patients, the follow-up was unsatisfactory. In an earlier study, McHardy et al[14] treated 134 patients with fumagillin, 60 mg./day for 10 days, and were able to follow 64 of them for four months or more. The distribution of therapeutic results is presented in table I.

TABLE I

Distribution of Therapeutic Results of Fumagillin Therapy

Type of involvement	No. intractable	No. without previous therapy	Recurrences
Acute amebic ulcerative colitis	0	12	2
Chronic amebic ulcerative colitis	2	16	0
Asymptomatic cyst passer	4	30	1

MacQuiddy[20] reported the results of treatment of 82 cases of amebiasis of all degrees of severity, of which unfortunately only a small proportion could be followed for prolonged periods. It was felt that 68 cases were definitely improved, 6 were definite failures, and 8 were inconclusive. At the end of three months' follow-up 29 of 32 cases were clear of *E. histolytica*. Oliver-Gonzales and Dobal[21] treated 26 cyst passers in Puerto Rico with fumagillin, 10 to 30 mg. daily for 10 days. Twenty-two of these individuals remained negative for at least three months' follow-up, whereas 4 persons relapsed between the fourth and the thirty-first day after therapy.

In the treatment of 20 cases of acute amebic dysentery, Armstrong[22] claimed an 85 per cent "cure" after 20 days. Morones[23] gave doses of 60 mg./day of fumagillin and, in three days, completely arrested the symptoms of 13 patients with acute amebic dysentery. Their stools became negative on the fourth day, and sigmoidoscopy performed three months after the completion of therapy showed no lesions and revealed no parasites. In 7 patients with rectosigmoid ulcerations treated by Hernandez de la Portilla et al[17] with fumagillin, 50 to 200 mg./day for 9 to 14 days, all were rapidly cleared, but 2 relapsed three months after therapy. Becerra and de Esesarte[24] had the same experience with this dosage level: 2 of 9 patients relapsed. A number of these authors point out that it is impossible to distinguish a relatively late relapse from a reinfection because the majority of their patients live in an environment heavily infected with *E. histolytica*.

Black et al[15] studied a series of 30 patients who had either trophozoites or cysts of *E. histolytica* in their stools. Seventeen of these patients were asymptomatic. All received fumagillin, 10 mg. three times daily for 14 days. In the asymptomatic group, all stools were negative at the end of treatment and six weeks later. In the symptomatic group, all 13 patients had negative stools at the end of treatment, 2 individuals were positive after one month, and the 5 patients seen after six weeks were negative. No follow-up was possible on the others.

Anderson et al[18] carried out a comprehensive clinical study on the treatment of amebiasis in children. Fifty-two episodes of amebic infection in children were treated with either erythromycin alone, fumagillin alone, or the two drugs administered simultaneously.

Erythromycin, 300 mg. daily for 14 days, permitted 2 relapses in 17 treated individuals. Fumagillin, 10 to 40 mg. daily for 14 to 18 days, resulted in 6 relapses in 14 treated individuals. When the two drugs were employed together in similar

doses, there were 5 relapses in 21 treated cases. The authors concluded that no true synergism had been demonstrated between erythromycin and fumagillin. However, with repeated courses of the two drugs, amebic infection was eradicated in all but 1 of their patients. While fumagillin is probably not the drug of choice for the treatment of amebiasis in children, it may be a valuable drug in those cases that are resistant to other forms of therapy.

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BLOOD TEST FOR ARTHRITIS. A new test to diagnose rheumatoid arthritis, announced by Dr. Ronald W. Lamont-Havers, associate medical director of the Arthritis and Rheumatism Foundation, was made available to physicians early this year. The test is based on the fact that sensitized sheep blood cells will clump when in contact with blood from a patient suffering from rheumatoid arthritis. Physicians are invited to send patient's blood serum to the Grace-New Haven Hospital, New Haven, Conn., to be tested.

NEW TREATMENT FOR RHEUMATISM. A new treatment for the rheumatic shoulder-arm syndrome, injecting novocaine into cervical muscles, is reported by Dr. Claude N. Lambert, head of the department of orthopedic surgery at the University of Illinois College of Medicine.

EMOTIONAL DEPRIVATION AS STRESS. Evidence that emotional deprivation in childhood can act as a "stressor" agent is presented by Dr. Rene A. Spitz in the "Fifth Annual Report on Stress" (edited by Drs. Hans Selye and Gunnar Heuser), published this month by MD Publications, Inc. The book also contains a summary of the latest laboratory and clinical findings on stress and includes a study of this important new medical concept in the physiologic, endocrinologic, and therapeutic fields.[1]

UROLOGY AWARD. The American Urological Association offers an annual award of $1000 (first prize of $500, second prize $300, and third prize $200) for essays on the result of clinical or laboratory research in urology. The first prize essay will appear on the program of the forthcoming meeting of the Association at the Statler Hotel, Boston, Mass., May 28-31, 1956.

ISONIAZID PROPHYLAXIS. Isoniazid in drinking water has proved prophylactically effective in preventing deaths from tuberculosis in guinea pigs, according to experiments reported by the National Tuberculosis Association. Large numbers of guinea pigs were given isoniazid in their water prior to infection with tubercle bacilli. After 10 weeks of treatment many of the animals were still alive and there was no interference with their weight.[2]

GRANT FOR POLIO RESEARCH. The National Foundation for Infantile Paralysis has made a grant of $200,797 to the University of Cincinnati and Cincinnati's Children's Hospital Research Foundation for continued research for a live virus vaccine, under the direction of Dr. Albert B. Sabin, the university's professor of research pediatrics.

NEW RESEARCH INSTRUMENTS. Investigators of The Upjohn Company, Kalamazoo, Mich., have developed two new automatic instruments to aid pharmaceutical research: The "ouch meter" tests physical reaction to pain to obtain accurate evaluations of analgesics. The "automatic bacteriologist," called an automatic recording nephelometer, checks and records the growth of 300 tubes of cultured microorganisms every two hours, around the clock.

ALCOHOL ADDICTION STUDIED. At Northwestern University medical school, Drs. G. K. Yacorzynski and Harvey Nash are directing a study on the effect of alcohol on the ability of a person to cope with emotional problems. The department of neurology and psychiatry received a grant for $26,000 from the Illinois department of welfare to begin the study.

NEW SEDATIVE DEVELOPED. A new nonbarbiturate hypnotic and sedative drug known as pentaerythritol chloral is reported by Dr. Robert L. Gatski, medical superintendent of the Danville State Hospital, Danville, Pa., to bring sleep in 15 to 20 minutes lasting up to 8 hours with no evidence of habituation, hangover nausea, circulatory disturbance, or mental depression.[3]

EKC VIRUS ISOLATED. Dr. Ernest Jawetz, head of a research group at the University of California Medical Center, has isolated the EKC virus (epidemic keratoconjunctivitis), designated as Type 8 of the adenoidal-pharyngeal-conjunctival (APC) group of organisms.

SALK TESTING NEW VACCINE. Dr. Jonas E. Salk is supervising large-scale tests launched this year of new polio vaccine preparations on kindergarten and first grade students in 13 Pittsburgh schools. The new vaccine is more potent than the one now in use, containing more virus particles per unit volume.

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International Council on Health and Travel

The International Council on Health and Travel was formed in 1955 as a result of the great interest aroused by the First International Symposium on Health and Travel,* held in New York City, June, 1955. This Symposium, which was attended by physicians from the United States and abroad, received wide coverage in the lay and medical press. A wealth of sound advice, not available elsewhere, was offered for the general practitioner, internist, pediatrician, and gynecologist. The gastrointestinal and cardiovascular systems were thoroughly explored and the special needs of women and the young, aged and ill were brought into focus. In addition, the clinical problems raised by travel, such as motion sickness and motion sensitivity, were presented with descriptions of their successful treatment.

Through this Symposium, a new branch of medicine was created: Travel Medicine. And it is to Travel Medicine that the International Council on Health and Travel is dedicated. Besides endeavoring to protect the health of travelers of all ages and studying health and environmental factors in specific geographical areas, the Council will serve as a permanent committee to act in an advisory capacity to the medical profession and the pharmaceutical industry. Research, study projects, and symposia will be sponsored by the Council.

The Scientific Advisory Board of the Council includes most of the distinguished physicians who presented papers at the First International Symposium on Health and Travel, and the board will be expanded gradually to include other outstanding clinicians from Europe, Latin America, and Asia.

The present members of the Scientific Advisory Board are the following well-known authorities: Herman I. Chinn, Ph.D., Chief, Dept. of Pharmacology-Biochemistry, USAF School of Aviation Medicine, Randolph Field, Texas; William T. Foley, M.D., Assistant Professor of Clinical Medicine and Chief of the Vascular Clinic, New York Hospital, New York City; Gaétan Jasmin, M.D., Institute of Experimental Medicine, University of Montreal, Montreal, Canada; I. Newton Kugelmass, M.D., Sc.D., Consultant, Dept. of Health and Hospitals, New York City; Elmer H. Loughlin, M.D., Associate Clinical Professor of Medicine, New York Medical College, Flower & Fifth Avenue Hospitals, New York City; Félix Martí-Ibáñez, M.D., Editor of INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS; Jacques M. May, M.D., Head, Dept. of Medical Geography, American Geographical Society, New York City; Hubertus Strughold, M.D., Ph.D., Chief, Dept. of Space Medicine, USAF School of Aviation Medicine, Randolph Field, Texas; William L. Wheeler, Jr., M.D., Medical Director, W. R. Grace & Co., New York City.

The INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS is the official organ of the International Council on Health and Travel.

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* The following presented papers at the First International Symposium on Health and Travel: Walter C. Alvarez, Herman I. Chinn, William T. Foley, Gaétan Jasmin, I. Newton Kugelmass, Elmer H. Loughlin, Félix Martí-Ibáñez, Jacques M. May, Miriam E. Perry, Hubertus Strughold, and William L. Wheeler, Jr. The proceedings of this Symposium will be published in March, 1956, as a case-bound book entitled "Health and Travel" by MD Publications, Inc.

The Lung Cancer Puzzle

The etiology of lung cancer is like an unfinished jigsaw puzzle composed of pieces that are recognizable but that never quite fit together. This singular elusiveness may be attributed to the fact that the lungs are in intimate contact with the outside world and are, therefore, exposed more than any other organ to a variety of environmental factors. This survey of some of the known or suspected etiologic agents in bronchiogenic carcinoma will show what is meant.

The widespread interest in lung cancer stems from the disquieting fact that in the last 20 years the male death rate from this specific disease has more than quadrupled in the United States; during the same period the death rates from cancer of the stomach, prostate, rectum, and liver remained virtually stationary or declined to some degree. The World Health Organization statistics for 15 countries,[1] established for the years 1949 to 1952, also show a considerable increase in the male rate of death from cancer of the respiratory system. These two sets of data, like all statistics, are fraught with pitfalls of interpretation. The WHO report, for example, notes that modern techniques of diagnosis, improved roentgen-ray examination, and the new cytologic method of diagnosis may have raised the number of reported lung cancer cases.

CANCER AND RESPIRATORY DISEASE

One of the more controversial aspects of lung cancer is whether this disease is connected with respiratory tract infections or lesions. Dr. Walter Finke, in this issue, supports the view that chronic pulmonary disease may be one of the "nearer causes" of bronchiogenic carcinoma. His statistical study can be correlated with Raeburn and Spencer[2] who reported a close histologic association between the site of the origin of cancer and lung fibrosis and bronchiectasis. On the other hand, the obvious difficulty of obtaining evidence from the history of many lung cancer patients has caused some investigators to doubt the existence of any relationship between cancer and respiratory diseases. As long as we do not know how a normal lung cell is transformed into a malignant one, this etiologic factor will have to remain in suspense.

ENVIRONMENTAL HAZARDS

We are on firmer ground when it comes to the etiology of lung cancer among persons engaged in certain industries or occupations. There is now ample evidence of a definite risk of lung cancer among workers in the nickel, asbestos, chromate, and coal gas industries, and among miners of hematite and certain radioactive ores.[3]

It is interesting to note that most of this knowledge is fairly recent, as 25 years ago our understanding of industrial cancer hazards was limited to the arsenicals, coal tar, and petroleum distillates.

It is also only fairly recently that investigators have tackled the problem of lung cancer in relation to air pollution. A number of studies[4–6] have shown that the mortality rate from lung cancer is consistently higher in urban than in rural areas. In almost every case, the mortality is shown to increase with the density of urbanization. It can be argued that city slums breed persons with weaker constitutions and less resistance to respiratory tract diseases. On the other hand, the presence of known carcinogenic agents in polluted town air cannot be lightly disregarded.

Quite recently it has, in fact, been confirmed that chimney smoke and the exhaust fumes of motor vehicles contain 3,4-benzpyrene, a hydrocarbon compound that easily induces malignant growths in experimental animals. The studies of Kotin and co-workers[7] on the composition of the notorious Los Angeles "air" are noteworthy in this field. All in all, it has been estimated that human lungs in a typical large city breathe in some 200 micrograms of benzpyrene per year, which is a sizable number of carcinogenic molecules. Moreover, the large increase in the number of motor vehicles (cars, buses, and trucks) in the last 15 years has sprayed millions of carcinogenic carbon particles into the air from the erosion of tires on asphalt surfaces. While some of these are undoubtedly stopped by the nasal filters, many must find their way to the bronchial epithelium, where it is quite possible that they produce irreversible chemical changes in cells.

THE ROLE OF TOBACCO

The controversial problem is raised of a possible relation between smoking tobacco and lung cancer, particularly as the carcinogenic benzpyrene found in polluted air is also present in cigarette, cigar, and pipe smoke. The residue found in the filtrate of tobacco products also yields anthracene, pyrene, 1,12-benzperylene, and arsenic trioxide, the latter probably derived from insecticides sprayed on tobacco plants. But there are about 50 other compounds present in tobacco and cigarette paper that have not yet been tested for carcinogenicity.

No one can gainsay that lung cancer death rates have climbed steadily throughout many nations in the last 20 years, and this has been correlated with the increase in smoking. It could, in truth, be correlated just as easily with the increase in the number of motor vehicles or the pollution of urban-industrial air by a variety of new chemicals. The history of medicine is strewn with spurious correlations from which the weirdest theories have sprung.

The best known of the statistical studies done here and in Britain, on the relation between smoking and lung cancer, have been challenged recently by Berkson, leading statistician of the Mayo Foundation.[8] On the basis of the published British and American studies, Berkson pointed out that the real question was not: "Does cigarette smoking cause lung cancer?" so much as: "What disease does cigarette smoking not cause?"

On the other hand, it is entirely possible that smoking tobacco in any manner or form may aid the development of chronic bronchitis, as shown in the most recent study of two Brompton Hospital clinicians.[9] In this case, we would return to the study of Finke which shows that any type of insult to the pulmonary tissues may

predispose a person to the development of a malignancy. Smoking would then be merely one link in the etiologic chain.

CANCER AND RADIATION

In the hunt for the etiologic factors of lung cancer, it is frequently forgotten that during the last 25 years or so there has been a rapid growth in the use of roentgenography of the chest, both for diagnostic purposes and in routine chest examinations. We have seen enthusiastic large-scale programs for the prophylactic examination of school children, Army inductees, factory and office employees, and miscellaneous adults.

A few years ago we were not aware that all forms of ionizing radiation, whether from a roentgen-ray machine or cosmic rays, could cause profound changes in the electrochemical balance of cells. These can occur by a direct disturbance in the arrangement of the atoms in cell molecules (enzymes, amino acids, nucleic acids) by transforming the water inside and outside a cell into hydrogen peroxide, or by some other mechanism we have not yet discovered. It is a sadly notorious fact that physicians and radiologists have a higher incidence of leukemia than the ordinary population, blamed on their constant exposure to roentgen-ray apparatus. Could not routine chest examinations also share part of the blame for the increase in lung cancer deaths? Early diagnosis with Roentgen's wonderful machine helped to tumble the death rate from tuberculosis, it is true, yet we cannot be certain that it did not concurrently raise the incidence of bronchiogenic carcinoma.

We are thus faced with two sets of possible etiologic factors in lung cancer: first, the endogenous ones of hereditary weakness, the belated effects of the colossal 1918 to 1920 influenza epidemic, chronic bronchitis or bronchiectasis, and some possible endocrinologic factors we know not about; secondly, the exogenous influence of polluted air leading to chronic pulmonary disorders, identifiable carcinogenic chemicals in the environment, and natural or man-made forms of ionizing radiation. As we are learning more clearly every day, it is dangerous to attempt to blame any disease on a single etiologic factor. The lungs are the living link between our inner physiologic milieu and the outer world; all forms of internal and external stress must, therefore, be viewed with healthy suspicion if we are to conquer lung cancer as we have already mastered pulmonary tuberculosis.

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Definition of "Antibiotic"

Selman A. Waksman, Ph.D.

NEW BRUNSWICK, N. J.

Antibiotic, n. A chemical substance produced by microorganisms that has the capacity, in dilute solutions, to inhibit the growth of other microorganisms or destroy them. Vuillemin, in 1889, first defined the words *antibiosis* and *antibiotic*, as pertaining to the injurious effects of one organism upon another. These effects were later found to be due largely to the production of specific chemical substances. In 1942, Waksman designated these substances as antibiotics. The most important of the early antibiotics, discovered prior to 1939, were pyocyanase, gliotoxin, *Bacillus mycoides* factor, and penicillin, the last described by Fleming in 1928. In 1939, Dubos isolated from a soil bacillus tyrothricin, which was found to be active largely against gram-positive bacteria, both in vitro and in vivo. This was soon followed (1940) by the reisolation of penicillin in pure form from cultures of molds (*Penicillium*) by Florey, Chain, and their assistants, and by the isolation of a group of antibiotics from cultures of actinomycetes (actinomycin, 1940; streptothricin, 1942; streptomycin, 1943) by Waksman and his assistants.

Antibiotics are produced by aerobic spore-forming (tyrothricin, bacitracin, polymyxin) and non-spore-forming bacteria (pyocyanase), by filamentous fungi (penicillin) and higher or mushroom fungi (polyporin, clitocybin), and by actinomycetes (actinomycin, streptomycin, chloramphenicol, tetracyclines). Antibiotic-like substances are produced by higher plants (quinine, emetine, tomatin) and animals (lysozyme).

More than 500 antibiotics are now known. Only about 20 of these have found extensive application in the treatment of infectious diseases in man and animals. Since the discovery of penicillin, the most important new antibiotics were found to be produced by actinomycetes. The manufacture of antibiotics has now grown to a great pharmaceutical industry, sales amounting to more than 500 million dollars annually in the United States alone.

The antibiotics differ greatly in their physical properties, chemical composition, antimicrobial activities (antibiotic spectrum), toxicity, and usefulness as therapeutic agents. Some are active only upon bacteria, others upon fungi, still others upon bacteria and fungi; some are active on viruses, some on protozoa, and some are also active on neoplasms.

Penicillin is most effective against infections caused by various gram-positive bacteria and cocci; in the treatment of syphilis and gonorrhea, it has replaced most of the earlier medications. Streptomycin is effective against a variety of bacterial diseases resistant to penicillin, notably those caused by gram-negative bacteria (tularemia, plague, intestinal infections), and tuberculosis. It is now also used extensively in combination with penicillin and with purely chemical compounds, such as *p*-aminosalicylic acid and isoniazid.

Among the other antibiotics, chloramphenicol, the tetracyclines, bacitracin, neomycin, polymyxin, viomycin, erythromycin, and carbomycin are very important

as therapeutic agents. Some of these substances have a somewhat wider range of activity than penicillin and streptomycin, being active also upon rickettsial diseases (typhus, Rocky Mountain spotted fever) and those caused by larger viruses (psittacosis).

Antibiotics can now alleviate most bacterial infections. They are finding extensive applications in veterinary medicine and in the treatment of certain bacterial and fungus diseases of plants (fire blights of fruit trees and blights of beans, tomatoes, peppers, and tobacco). Antibiotics also possess certain growth-promoting properties and are being used extensively in the feeding of nonherbivorous animals. They also find application in the preservation of biologic materials (bull semen, virus preparations).

The extensive use of antibiotics in the treatment of various infectious diseases tends to favor the development of resistance among sensitive organisms. They also exert certain toxic reactions, depending upon the particular substance, nature of the disease, and method of treatment. Impairment of hearing and dizziness may be due to excessive doses of streptomycin; allergic reactions may be brought about by penicillin; varying degrees of nausea, vomiting, and diarrhea may be caused by tetracyclines. An increasingly important effect of certain antibiotics, given orally, is the appearance, during treatment, of fungus infections. The introduction of antifungal antibiotics (nystatin, trichomycin, candicidin, candidin) will tend to correct such conditions.

Can chlortetracycline be used for prophylactic indications?
Is erythromycin useful in genitourinary infections?
Do children tolerate intramuscular oxytetracycline?

These questions, among many others, continually arise in private and hospital practice. The field of antibiotic medicine is constantly expanding. New antibiotics are being developed, and new uses are being found for the older antibiotics.
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FOOD AND DRUG ADMINISTRATION ANNIVERSARY EDITORIALS

In June of 1956, the Food and Drug Administration will have completed fifty years of service to this nation. In order to pay tribute to the outstanding achievements of the FDA, Antibiotics & Chemotherapy, Antibiotic Medicine, *and the* International Record of Medicine and General Practice Clinics, *journals of MD Publications, Inc., are publishing a series of exclusive Editorials written by members and associates of the Food and Drug Administration on the various activities and different facets of the technical work that is carried on.*

Claims for Vitamins

E. M. NELSON and O. L. KLINE

Food and Drug Administration
Division of Nutrition

Claims of benefit from the use of vitamins for all ills continue to increase, with no sign of a plateau in sight. Scientific information developed during the last decade has given us a basis for understanding the needs for the vitamins in human nutrition, and something of their physiologic functions, and it is important to point out the educational need for a common sense point of view toward this problem.

Vitamins must be considered as nutrients, along with the other constituents of food, i.e., carbohydrate, fat, protein, salts, and water. A complete lack of any one of these substances causes dire changes in the metabolism of the experimental animal. This metabolism is normal when adequate amounts of these constituents are consumed, and excesses, within limits, are neither harmful nor beneficial.

Human requirements for the vitamins are set forth in the form of Recommended Dietary Allowances published by the Food and Nutrition Board of the National Research Council. These figures are for the amounts of each of the vitamins that must be present in the diet to meet the needs of a wide variety of individuals. It is not difficult to meet these requirements with the goods available in the grocery store. In fact, it is fair to assert that for the most part the American population does obtain its vitamin requirements in this way.

There are instances, of course, where vitamin products are prescribed and used with good reason. In this country the age of outright vitamin deficiency disease in the adult, seen during the depression days of the 1930's, is past, and the well-informed physician must look closely to determine whether or not symptoms and signs observed indicate faulty nutrition.

Even so, the less than scrupulous purveyor of vitamin products continues blatantly to call attention, in every possible medium, to the likelihood that "that tired feeling," stress of many kinds, or being run-down indicate subclinical defi-

ciency and the need for vitamin supplementation of the diet. The nature of claims made to promote the sale of an article has undergone a gradual change, since the Food and Drug Administration has been successful in court against openly misleading claims. It is no longer a common practice to say "Our product is guaranteed to cure all skin diseases or your money back." Such a statement is too easy to disprove. Now the purveyor of such an article uses clever qualifications that lead to double talk, or he may even go so far as to state the specific conditions under which a product will not be effective, with the implication that under conditions other than those specified, it is effective. Scare technique of emphasizing dangers to health are still common weapons, not confined to the printed page, but used also by door-to-door salesmen and health food lecturers.

Vitamin deficiency, the artful copywriter states, is the result of depleted soils that produce foods of inferior nutritive value. This has been refuted by sound scientific evidence except for the case of iodine. He implies great losses of vitamins in food processing, transportation, storage, and cooking. Bear in mind that in home cooking before the last generation there was little knowledge of how to prevent these losses. But in the modern processing of food, it is in the best interest of the manufacturer to know of and to prevent such losses and to provide a food of highest possible nutritive value. Better methods of home cooking also are in wide use. Highly questionable are the claims of benefit for so-called unidentified nutritional factors said to be present in a few milligrams of a concentrate prepared from natural plant sources. If such factors exist, how much more likely it is that they will be obtained by consuming the natural foods themselves. Claims for great value of high potency therapeutic vitamin dosage are presented with such force and volume that the patient, we are told, now demands of the doctor treatment with vitamins he has heard and seen described.

Various kinds of stress are said to increase the need for vitamin supplementation, with every change in our environment and every change in food or water intake subjecting the living body to a stress that must be overcome by the intake of extra vitamins. Why? We hunt in vain for some evidence to support this vague theory. In a recently stated concept of stress by Dr. Selye, it has been defined as a nonspecific deviation from the normal resting state caused by function or damage, which stimulates repair. The endocrine and nervous systems are most important in this response, and it is suggested that the adrenal cortex and the anterior pituitary are the great co-ordinators. In efforts to increase the sale of vitamin products, this concept is extended to imply an increased nutritional requirement in stress. We can find without difficulty data that tell us this application is not valid. In fact, the theory would just as well permit the conclusion that an excessive intake of vitamins would produce stress.

The stress of infection has been a particular focal point in vitamin claims. It is proposed that vitamins are an aid in the prevention or treatment of infection. That there is no established value of vitamins in this relationship was well stated in the summary of a recent symposium on nutrition in infections: "That the papers presented here are a heterogeneous lot is, I think, almost an historical necessity, for it is now more obvious than ever that there is no clear and simple

connection between infection and nutrition that has won universal assent." In the same vein, Goldsmith has concluded that the influence of vitamin nutrition on resistance to specific infections in the human subject remains largely unknown. Further, the paucity of information relative to the efficacy of antibiotic-vitamin combinations precludes any attempt to evaluate this method of therapy at the present time. She states finally that there is no magic formula that can relieve the practicing clinician from the detailed analysis of all facets of the patient's nutritive state.

The daily diet, if taken in sufficient amounts to supply the needed energy and protein, under most conditions will supply the vitamins necessary to utilize that energy and protein. There are conditions that the physician with care will recognize, which require a supplemental intake of vitamins, either for nutritional or psychologic reasons, but this does not imply or support the claim that deficiency disease is widespread. Vitamin products, used intelligently and with some degree of common sense and understanding, have a definite place in medicine.

Self-styled nutritionists, on the other hand, should not be treating disease or persuading the public to use "health foods" for conditions requiring rational medical care. The Food and Drug Administration has been able to take court actions when a definite association can be established between false claims (either oral or written) and a specific product. The situation can be met only by public education, however, when the propaganda is spread by books, magazine articles, general lectures, and other means beyond the reaches of the Federal law.

Economic Cheats and the Law

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In the crude old market game of "thumb on the scales," not often played any more, the contestants at least faced each other squarely. In retrospect, there seems almost a tinge of sportsmanship in the way the even then infrequent cheater accepted some risk of discovery, knowing full well that the observant buyer, alert to the philosophy of *caveat emptor*, was being afforded a chance to protect his own interests.

It is common observation these days that progress in commodity distribution has brought with it a minimization of those personal contacts and a gradual disappearance of those simpler mechanics of retail trade that formerly often provided the customer some opportunity to exercise his own resources in pursuit of his own money's worth. Moreover, these changes have clothed the purveyor in a kind of anonymity, and it is a remarkable characteristic of human behavior that people will tolerate imposition at the hands of a remote uncertain perpetrator, which they would not abide from an identifiable neighbor. Fortunately, and doubtless in enlightened recognition of what constitutes good business, there has

been concurrent improvement in industrial and mercantile practice, having the effect of generating a consumer confidence well-merited by the great bulk of the nation's food and drug supply. Paradoxically, this favorable development presents the few remaining chiselers an enhanced opportunity, for it is manifestly basic to the practice of fraud that people can more readily be swindled if their trust be first secured.

The unscrupulous are aided also by the relative ease with which substitution and inferiority may be concealed from ordinary observation in today's processed, compounded, packaged foods. So, likewise, is it easy, in the aura of current nutritional and therapeutic progress, to capture general credulity for those exaggerated and baseless claims of benefit that the "gyp artist" will ascribe to common foods and impotent nostrums.

Lincoln once said something to the effect that good government exists to do for the citizen what he cannot do for himself. The Federal Food, Drug, and Cosmetic Act is an instrument of that kind of government. Among its provisions are those designed to protect the public from economic victimization by the relatively small segment of the food and drug industries that may be disposed to traffic in debased and misrepresented goods. Of no small related significance, to the bulk of those industries, is the salutary influence of these provisions of the act in mitigation of disruptive trade practice represented by the activity of this minor fraction of their fellow businessmen. For their comparative number is evidently few; yet, obviously, the share they can steal of this 50 billion dollar annual commerce could well be minute indeed, and still account for a huge amount of groceries and medicine.

In the first order of cheater-prevalence is, no doubt, the short-weighter. The adulterant he uses is that most commonly available—free air. But it's not so free in the guise and at the price of even the most inexpensive food.

Dilution is next in prominence, palming off tap water in lieu of part of the product. The fact that water is a normal component of most foods makes it often easy to add some more without ready detection.

Since these adulterants, air and water, cost nothing, the entire substitution is clear profit. Recognizing that profit in the food industry does not ordinarily exceed a small per cent of gross value of production, it is evident that proportionate profit increase consequent to comparatively minor weight shortage, or relatively small dilution, may become tempting indeed.

The up-graders march third in this parade of rascals. By false promise of higher than actual quality, they also get something more, for absolutely nothing in return.

There are other, more subtle and ingenious, types of cheat, too many here to record. But mention must be made of the meanest of all, the false claim of nutrient or therapeutic benefit. Good, cheap, wholesome food products, that are nothing more than that, are recurrently exploited as modern miracles. At exorbitant charges, common mixtures of vitamins and minerals, virtuous enough in their own limited right, are peddled as boons to mankind; and worthless nostrums are extolled as lifesavers, in the lowest form of misrepresentation. Conscienceless fakers ply their trade in such as these with all the trappings of last century's "medicine

man." Their pitch is obviously directed to the weak and the ill, those most to be harmed by their vicious deception.

Obviously the individual citizen is not prepared to avoid the swindlers of these ilks. It therefore becomes the obligation of government to hold them in check through effective enforcement of provisions of law adequate to these ends.

New Drugs

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There were no restrictions to the introduction of new, untested, or dangerous drugs into interstate commerce prior to June 25, 1938, and the enactment of the present Food, Drug, and Cosmetic Act. As a result, the "Elixir Sulfanilamide Tragedy" with more than 108 deaths took place, and called the attention of the country to the need of additional legislation to protect the public from similar disasters.

"Elixir Sulfanilamide" was the result of marketing a diethylene glycol solution of sulfanilamide without any investigation into the toxicity of the solvent. Sulfanilamide is not readily soluble in the ordinary safe solvents, and so diethylene glycol was used. Diethylene glycol was subsequently demonstrated to be highly poisonous to all animals tested, so even a simple preliminary animal toxicity test would have precluded its use. With the sudden wave of deaths reported throughout the country, the Food and Drug Administration promptly investigated and arrived at the conclusion that "Elixir Sulfanilamide" was the deadly agent.

Without legal authority to take action on the dangerous drug, the Administration turned its entire inspection force toward the recall and recovery of the drug before more people were killed. This was done on the basis that elixir sulfanilamide was misbranded, inasmuch as it was not an "elixir," that is an alcoholic solution, but a diethylene glycol solution.

New Food and Drug legislation had been introduced in numerous sessions of Congress, but failed to pass. However, with the "Elixir Sulfanilamide" tragedy as a spearhead, the Federal Food, Drug, and Cosmetic Act of 1938 was enacted with provisions that all "new drugs" must be shown to be safe for use prior to marketing.

The term "new drug" was, by this law, given a legal definition, and an application was required. In the application, full details of the investigations conducted to evaluate the drug's safety, its components, the method of manufacture, and controls were required. Responsibility fell on the Food and Drug Administration to evaluate all applications and determine whether they were complete, whether adequate study had been conducted to evaluate the safety of the preparations, and whether the articles could be safely used.

Some of the pharmaceutical industry felt that progress would be stifled, since it was well recognized that practically any potent drug had dangerous potentialities.

However, the Food and Drug Administration has always weighed the therapeutic value of the drug against its toxicity and has given particular attention to safeguards, such as informative labeling to warn physicians against potential dangers. As a result, pharmacologic and clinical research have become important fields in many of the leading medical institutions.

The results are reflected through the most startling advancements in medicine. New drugs, which have been evaluated by the Food and Drug Administration, now account for more than 90 per cent of all the prescriptions written today. Many dreaded diseases are now readily treated. Pneumonia is no longer the "captain of death." Syphilis is rapidly and effectively treated by penicillin. Treatment of tuberculosis has been simplified through streptomycin, isoniazid, and *p*-aminosalicylic acid. A few micrograms of vitamin B_{12} can reverse the development of pernicious anemia. Adrenocorticotropic hormone, cortisone, and other corticosteroids may be lifesaving and aid in the rehabilitation of many. Progress has been made in the treatment of hypertension, mental disease, and malignant disease. Pharmacology, which formerly was considered a minor subject in many medical schools, is now recognized as among the most important.

More than 10,000 new drug applications have been reviewed by the Food and Drug Administration. Working under a strict time limitation of 60 to 180 days and under severe handicaps of insufficient staff, the New Drug Branch of the Food and Drug Administration has accomplished an outstanding service in the field of public health.

The Why of Prescription Drugs

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In the debate that preceded passage of the Durham-Humphrey law, an amendment to the Federal Food, Drug, and Cosmetic Act that defines the types of drugs that must be restricted to prescription sale, there was quite general agreement that many of the modern drugs could be used with relative safety only under professional supervision. Much of the controversy over that amendment arose, not over its fundamental purpose, but over how that purpose could be accomplished without placing undue restrictions on the manufacturers, distributors, and users of drugs—particularly the professional people, pharmacists, and physicians.

It may well be said that the legal restrictions on the sale of certain drugs without prescription is a logical and necessary outgrowth of the golden age of medical discovery in which we live. A few decades ago, there were a relatively small number of drugs available that were likely to cause serious harm when used by the public for attempted self-medication. Aside from the narcotics (controlled under separate legislation), there were virtually no drugs in serious demand for nonmedical use.

The original Federal Food, Drug, and Cosmetic Act of 1938 proved reasonably

effective in bringing about the removal of dangerous drugs from proprietary remedies promoted for direct sale to the public. This was accomplished under a provision of the Act that prohibited the distribution of a drug that could not safely be used in the manner recommended in its labeling. The original Act, however, did not deal forthrightly and specifically with the restriction of drugs to prescription sale. Attempts to accomplish that by regulations promulgated under the law were not altogether satisfactory, either to the administering agency or to those regulated.

The new-drug section of the 1938 law provided that a manufacturer could not distribute commercially any new drug until he had submitted to the Food and Drug Administration convincing evidence that it was safe to use in the manner recommended in its labeling. This provision would be virtually impossible to administer without an enforceable prescription restriction. The new-drug section must reach a determination that the usefulness of the drug outweighs its potentiality for harm before it can be released. Evidently it would be difficult to reach such a conclusion about many of the newer drugs if they could not be restricted to prescription sale but had to be released for indiscriminate use and promotion to the lay public.

Increasing misuse and abuse of the newer potent drugs led to the passage of the Durham-Humphrey law. From our own experience before and since the passage of this law, in investigating the results of the misuse of drugs, we are convinced that this amendment is basically sound public health legislation and we believe it deserves the support of all in the health professions. When the measure was being considered by Congress, Dr. Walter P. Martin, testifying in behalf of the American Medical Association, gave the Association's endorsement to the majority of the objectives sought by the legislation, including those that were finally enacted into law. The bill also had the endorsement and has had the continuing support of the National Association of Retail Druggists.

Our correspondence indicates that there is some sentiment that the Food and Drug Administration arbitrarily restricts too many drugs to prescription sale. This criticism is balanced by other complaints that some drugs are released for over-the-counter sale without adequate evidence that they are safe for use in self-medication. The truth of the matter is that the administering agency has little room for arbitrariness in making decisions about what legally must be a prescription drug or an over-the-counter drug. We must operate within the framework of the law and Congress has established the public policy in this law that any drug that is safe enough to use for a condition that a layman can reasonably diagnose and treat must be labeled for sale without prescription. Conversely, it was the clear intent of Congress to restrict to prescription sale any drug that is, for whatever reason, not suitable for use in self-medication. In the last analysis it comes down to a question of the kind of testimony medical experts in the field involved can give about a particular drug. When some of the antihistaminic drugs were first released for sale without prescription, many of the physicians we consulted were dubious about whether it was in the public interest to release these drugs for use in self-medication; but, at the same time, they were unable to say that the drugs proposed for over-the-counter sale were not safe in the dosages recommended.

The question of whether they were really useful in colds was so controversial that it would have been hopeless to try to litigate that issue. The burden of proof of ineffectiveness is upon the Government; the responsibility of showing safety is on the distributor.

Current medical literature bears adequate testimony to the need for restricting many of the modern drugs to prescription sale. Even when drugs are used with the greatest care by professional people, drug injuries are a major problem.

Public Health Activities of the Food and Drug Administration

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The Food and Drug Administration, during the past 50 years, has provided protection of the public health and welfare as its fundamental responsibility and function through control of foods and drugs in interstate commerce. With the passage of the Federal Food, Drug, and Cosmetic Act of 1938, protection was extended to control new drugs, dangerous drugs, devices, and injurious cosmetics, and protection improved with respect to foods and drugs. With these additional safeguards, the physician is aided in his efforts to prevent and treat disease. The provisions of this law dealing with the disclosure of active ingredients of drugs, adequate directions for use, and warnings against misuse contribute to the intelligent purchase and use of drugs.

Safeguards against variations in the strength, quality, and purity of drugs are of fundamental importance. Similarly, the requirement that the labels of foods offered for special dietary use bear adequate information to inform the purchaser, enables the physician and consumer to evaluate the indications for use of such foods.

A major area of health service to the public is the processing of new-drug applications setting forth evidence of the safety of the drug as submitted by manufacturers. The gravity of appropriate handling of these applications before releasing the drugs for use is complicated by the statutory requirement that the review be completed within a limited, fixed time. With the increasing numbers of highly potent and effective drugs being submitted currently for consideration, public health is paramount in the decision to allow such drugs to be marketed.

An invaluable service to the public is the pretesting for purity and potency before distribution of six of the most important antibiotics and insulin, as well as certifying the safety of coal-tar dyes for use in foods, drugs, or cosmetics. Regulation of the retail sale of dangerous prescription drugs is another important health protection service furnished by the Food and Drug Administration.

During the past 20 years, chemotherapeutic agents have been introduced that

have changed the methods of prevention and treatment of many diseases. The availability of the sulfonamides and antibiotics under the new-drug provisions and certification sections of the Act has markedly influenced the treatment of such serious infectious diseases as streptococcal infections, syphilis, gonorrhea, and tuberculosis, with a rewarding reduction of mortality from these causes.

Despite all of the precautions taken, serious illnesses and injuries resulting from unsuspected defects in commercial products have been encountered. None of the products involved was suspected of causing harm until an appreciable number of persons had become ill. The frequency and seriousness of these occurrences have become a matter of concern to those in the Public Health Service and the Food and Drug Administration who have responsibility for protecting the public from injurious substances in foods, drugs, and cosmetics and for controlling diseases or injuries arising from ingestion of harmful foods, drugs, and other hazardous articles. A recent incident that was encountered and controlled was the appearance of *Salmonella* infections in infants, traced in 16 states to the feeding of dried egg yolk. The product was voluntarily recalled from the market by the manufacturer when it became apparent that the food was associated with the illness.

Another major nationwide incident was the investigation by the Food and Drug Administration of the association of blood dyscrasias with chloramphenicol, which resulted in modified labeling of this drug in the interest of the physician and his patient.

A third major event was the appearance of convulsions in infants maintained on a liquid infant food. This involvement was corrected by a change in manufacture of the product. In this instance, with reports of illness from the Arkansas State Board of Health, the Food and Drug Administration undertook an investigation that resulted in the recall from the market of all material bearing the codes associated with this type of illness.

These cases are not the first of their kind, but they typify the examples that point up the need for prompt reporting of any unusual occurrences of diseases or injury to responsible health officials in order to safeguard others and to bring about an early correction of the health problem.

The general use of the many potent and effective therapeutic agents now available emphasizes the need to learn promptly of any serious untoward effects associated with their use. Should adverse effects be encountered with a product and revealed to the Food and Drug Administration, necessary safeguards to protect the patient, the physician, the hospital, the drug manufacturer, and the distributor would be effectively carried out. This has led, in the past few months, to the Pilot Study on Reporting Adverse Reactions to Drugs sponsored by the Food and Drug Administration and American Association of Medical Record Librarians in cooperation with the American Medical Association and the American Society of Hospital Pharmacists. Through this study, methodology can be developed for continued general submission of reports as well as their evaluation, dissemination, and program development. This cooperative undertaking may serve as the basis for a wide extension of this activity at a later date.

With the decline of infectious diseases through immunization procedures and

improved sanitation measures, poisoning from household chemicals, including drugs, has come into focus more prominently as a health problem. The Food and Drug Administration has been engaged in this area since the passage of the Federal Caustic Poison Act in 1927. With the active participation of the American Academy of Pediatrics, the American Medical Association, the American Public Health Association, health departments, hospitals, pharmacists, the pharmaceutical and chemical industries, and governmental and voluntary health agencies, measurable inroads are being made. Additional recognized needs, however, should be implemented to provide optimal protection.

With the continued cooperation and advice of public health officers, physicians, and other professional experts, the public can be assured of safe and nutritious foods and safe and effective drugs and devices.

Therapeutic Devices and the Federal Food, Drug, and Cosmetic Act

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The term "device" is defined in the Food, Drug, and Cosmetic Act as "instruments, apparatus, and contrivances, including their components, parts, and accessories, intended (1) for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; or (2) to affect the structure or any function of the body of man or other animals." This definition clearly and concisely differentiates the device from drugs or other therapeutic or diagnostic measures.

The original Act of 1906 did not contain a provision for dealing with devices of any description. As time wore on, and while the Act of 1938 was in the process of preparation, it became clear that there must be a means for properly labeling devices intended for legitimate distribution and for dealing with the device that the fraud and quack could distribute and use. Thus, the provisions of the 1938 Act defining devices were born.

When the Act of 1938 became effective in all of its provisions, it became obvious that a monumental job confronted the Administration in the appropriate labeling of devices. This problem involved not only the quack type of device but the legitimate devices, such as the roentgen-ray and diathermy machines used by physicians, clinics, and hospitals. The labeling provisions of the Act referred directly to devices in the same sense that it referred to drugs. In other words, both adulteration and misbranding provisions referred to drugs and devices. An extensive study revealed problems in the distribution and use of devices that did not exist in the drug field. These problems required that regulations be drafted differing sufficiently from the drug regulations to provide for the problems at hand. This knotty problem has been adequately resolved.

At the same time, the problem of the quack devices was demanding attention. There were no precedents for developing legal cases in this field and many problems were encountered that were new and different in all respects. Most devices encountered at the outset were of an electrical nature. We soon learned that many of these gadgets required a study of electrical circuits that could not be carried out in our laboratories. It was necessary to add a physicist to our staff in order to fulfill our obligations in enforcing the pertinent provisions of the Food, Drug, and Cosmetic Act.

The devices encountered were of every description. Many were of a diagnostic type, to be applied directly to the patient or to make a diagnosis at a distance, for example, from a sample of blood, handwriting, urine, or sputum. Others were operated in the office of a quack. It followed that the long-distance diagnosis could be hooked up to a long-distance treatment for the many and varied diseases resulting from the diagnosis. The treatment was administered only after the payment of an appropriate fee.

These devices were often bizarre in character. Some of the quacks who operated from an office setup preferred a device with a multitude of dials, switches, and meters, none of which was of significance. Others preferred devices that showed flashing lights, buzzers, or bells to indicate the location of diseased areas. All of these machines had to be evaluated on the basis of physical characteristics and qualities and coordinated with accepted scientific facts.

Some of the devices that proved to be most troublesome, from an enforcement standpoint, did not fall into the above categories. One of the outstanding examples of this type was known as the "Virillium Tube," or "The Magic Spike." It was alleged to contain a potent substance and was worn attached to the clothing at one or another location, and its magic emanations cured just about all human ills. After lengthy and bitterly contested legal battles, this device was laid away. Another extensively promoted device was known as the "Spectrochrome," developed and promoted by an East Indian named Dinshah P. Ghadiali. This was a metal housing for an ordinary electric bulb, with a water container for cooling purposes. Attached were a group of colored glass squares arranged in slides so the light could shine through any of the slides or a combination of them. A chart was provided, dividing the body into areas corresponding to the various colored glass slides. The sick user consulted the chart, found the proper area and color combination, sat in front of the projector, and proceeded to be "cured." This was all intertwined with semireligious mumbo jumbo, diet, and living regimen. A school had been developed in connection with the promotion; the chosen disciples were given a course of instruction and then went out to instruct others in the proper use of the machine. After lengthy legal battles, interstate shipments of this contraption were eventually ended, and heavy penalties were imposed upon the promoter. Unfortunately, organized groups are still attempting to perpetrate the racket within the borders of a number of states.

The quacks and racketeers are ever sensitive to the times and the developments of the day. It was inevitable that, in our atomic-conscious era, the quack and racketeer would take advantage of a situation tailor-made for them. And so was

born the "Atomatrone"—a completely worthless gadget composed of a single radio tube hooked up to an ordinary piece of window screen. Why? No one knows the answer to that one, but it did have an impressive appearance. Incorporated was an ordinary ultraviolet electric bulb shining through a group of colored glass slides into two 1 gallon containers of water. The water was "irradiated" for a given period of time and then consumed in the treatment of every known disease including diabetes, "coronary disease," and cancer. Again, lengthy legal battles ensued before the distribution of these devices could be stopped.

Also in keeping with the times are the uranium caves, mines, and sand. Rooms and caves are lined with sacks of uranium ore and benches built for the "patients" to sit upon while receiving the benefits from emanations of the order of those of the luminous dial of a wrist watch. The financial consideration is based upon time of treatment, usually a certain amount per hour. This racket has been aimed at arthritics.

It has been possible to end this racket where the Food and Drug Administration has been able to establish the fact that there was interstate shipment of the uranium ore or sand. The mines, if uranium mines they are, do not fall within the scope of our activities.

We are assured, however, on long experience, that the quacks and racketeers will always come up with a new one. As new developments in the world of science become publicized and the public becomes conscious of these developments, the promoters of these often bizarre devices will not miss the opportunity for another and perhaps greater payday.

Quackery and the Law

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Quackery, as defined in the dictionary, refers to "charlatanry" as an alternate and well-applied term. It is further defined as a false claim to medical knowledge and treating the sick without knowledge of medicine or authority to practice. Those who have had intimate and prolonged experience in treating the sick learn that all parts of the dictionary definition apply.

It is always interesting to speculate upon the question, "Why a quack?" Only the quack himself may supply an accurate answer to this ever-present question, but it seems clear that there are three types of individuals engaging in quackery.

The first, and most vicious, is the individual who for money, and money alone, engages in the use and distribution of a preparation for the treatment and cure of human ills. He is the individual who has a callous disregard for the welfare of unfortunates who fall into his hands and is interested only in their money. The second type is the truly misguided and ignorant individual who is convinced he has a sure cure for certain ailments and will treat patients under any conditions or circumstances in order to demonstrate his great cure. It is true that this type

of person is interested in monetary returns and may hope to make his living from it, but his basic drive appears to be to convince the world of the merit of his wonderful remedy. The third type is the individual who has been frustrated in his desire to become a true practitioner of the healing arts and, by sketchy reading, has attempted to fit himself to care for the sick even though it must be under illegal circumstances.

The types of quackery run the gamut of all human ills. The cancer field has been exploited for many years and is being exploited at this time. The widespread publicity given to this disease in recent years has been necessary and has served a great and beneficial purpose but, like so many splendid endeavors, has had its ill effects. It is unfortunate, but true, that the campaign to make the public cancer conscious and to get people to their physicians for periodic examinations has indirectly served the purpose of the purveyors of worthless cancer remedies.

The diabetic field has been exploited in every way possible by purveyors of fake diabetic remedies. Some of these remedies have been composed of weeds and herbs and some of simple chemicals. The first line of attack in the diabetic remedies is to advise and insist that the patient discontinue insulin. In addition, the patients are further advised to eat anything they wish, and one well-known quack advised that large quantities of honey be eaten daily.

The food faddists, the arthritis experts, and the weight-reducing experts are all hard at work today. The rejuvenation experts had their day and had faded out of the picture prior to the development of testosterone. With the advent of that valuable drug, they returned in full force, but, fortunately, the resurgence was nipped in the bud.

How do the quacks operate? There is no set *modus operandi*, since each of the "specialists" has his own tried and true technique. Some operate behind the front of licensed practitioners. Some are licensed to practice the healing arts, and under the cover of their license, practice the crudest forms of quackery. Others operate as "lecturers," giving a series of well-advertised lectures in city after city. These lectures are ostensibly on health subjects, but the lecturer usually has a display at hand of whatever remedy or remedies he may be peddling at the time and the remedies fit neatly into his lecture. Some operate from town to town, setting up business in a hotel room and, by word of mouth, their presence and their specialty is made known. This type is usually "on the run," and is most often successful in leaving town just ahead of local authorities. The least troublesome, but dangerous nevertheless, is the individual, and usually an elderly resident of a locality, who has set himself up as an authority and will attempt to treat anyone who may come to him. This quack may or may not use drugs, but his usual armamentarium is a group of remedies he claims have been handed down in his family from generation to generation and that he alone may concoct. He may or may not charge a fee for his services, but he is always very grateful for any donations his patients may wish to offer.

Can the practicing physician be of assistance in this battle against quackery and the needless squandering of human lives? He can and he must! First, what information can a physician give his patients so that they may be able to detect a

quack? The remedy is always a secret one, discovered by the quack, and only he knows how to use it. He is persecuted by the "medical trust." The "medical trust" persecute him and deny his methods because they cannot afford financially to permit a real cure to be available. There is a direct or implied promise to cure and a direct and immediate attack on all recognized methods of treatment. They make adroit and powerful attacks on the medical profession and they attempt, too often successfully, to destroy the patients' confidence in their physicians and the methods employed by them. If the practicing physician can point out to his patients these outstanding earmarks of the quack, he will have taken one long step on the road to educating the public in evaluating the quack.

A cardinal point in this battle relates to the patient with cancer. Too many times the physician, at the termination of a course of treatment, has informed the family that he has done all he can do and the outcome is inevitable. Such a course, in too many instances, is tantamount to buying the patient a ticket to the nearest or most widely known cancer quack. The physician must keep this fact ever before him in his relations with these patients and in his handling of them and their family. If he can keep this very important fact in mind and continue his patient-physician relationship, he will have taken one more long step down the road to victory over the quacks and quackery.

The application of the Food, Drug, and Cosmetic Act to quackery is always difficult and sometimes impossible. The extent and types of quackery extant could not be contemplated at the time the present law was drawn and passed by the Congress. The Food and Drug Administration has made, and is making, every endeavor to apply present provisions of the Act to quackery as it exists today.

The Food, Drug, and Cosmetic Act, in a general way, cannot be applied until it can be proved that interstate commerce is involved. The law deals with labels, labeling, and the misbranding of drugs through labels and labeling. A drug is defined in the Act (in part), as an article intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals and, also as an article (other than food) intended to affect the structure or any function of the body of man or other animals.

The term "label" means a display of written, printed, or graphic matter upon the immediate container of any article. The term "labeling" means all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such an article (in interstate commerce).

Under "Prohibited Acts" of the Food, Drug, and Cosmetic Act appears the following:

"The following acts and the causing thereof are hereby prohibited: (1) the introduction or delivery for introduction into interstate commerce of any food, drug, device or cosmetic that is adulterated or misbranded."

The Federal courts have held that printed or graphic matter must not necessarily move in interstate commerce with a drug to constitute labeling if they come together at a common destination. The Federal courts have also held that oral representations for intended use may constitute labeling if the goods on sale have moved in interstate commerce. This latter point has been of great assistance in

dealing with the "pitchman" type of quackery and the so-called health lecturer.

In the battle to overcome the quacks, it has been necessary to prove misbranding of the drugs they use and also that interstate commerce is involved. The quack need not personally ship the drug in interstate commerce, but, if he hands it to a patient going to another state, he has "delivered for introduction into interstate commerce."

In preparing a case against a quack, a number of points must be established: (1) that a drug as defined in the law is involved; (2) that interstate commerce is involved beyond a shadow of a doubt; (3) that labeling is in use and that it and the drug have come together at a common destination after moving in interstate commerce; (4) that the labeling serves to misbrand the drug by making false and misleading representations; and (5) when all of these data are obtained, the case must be presented before a Federal judge or a judge and jury.

To gather all of the material necessary to make a solid case that can stand up in court takes a tremendous amount of time and work by the administrative, inspectional, and medical staffs, each of which plays an important and integrated part in development of the necessary evidence. The quacks, however, are very helpful in many instances. They cannot exist and prosper in the manner to which they have become accustomed without the use of promotional material, such as booklets, leaflets, and testimonials. All of this material may, under the proper circumstances, be considered labeling that serves to misbrand the drug. When the evidence is considered to be sufficient to prove our case, it is submitted to the Department of Justice, which presents the case in court with the advice and assistance of the proper Food and Drug Administration officials.

The Food and Drug Administration has developed many successful legal cases against quacks of all types. Our endeavors have been hampered by a lack of funds, owing to budgetary restrictions, but we are continuing in the work with all of our available resources.

The Food and Drug Administration Physician

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"I will use treatment to help the sick according to my ability and judgment, but never with a view to injury and wrong doing." So wrote Hippocrates almost 25 centuries ago. Today the Federal Food, Drug, and Cosmetic Act is but a legal reaffirmation by the Congress of the United States of the fundamental validity of this great physician's teachings. Our present Federal law recognizes the obligation to treat and to help the sick but to do so with drugs of integrity and safety. It is within the confines of this principle that the Food and Drug Administration physician must function. Notwithstanding the varied duties and responsibilities in the Administration, first and foremost the individual is a physician. And so he must

remain if he is to play an active role in the medical phases of the administration of the food and drug law.

Contrary to the common belief that working for the government represents a relinquishing of professional stature and prerogatives, the physician in the Food and Drug Administration finds an opportunity for complete fruition of his highest professional ideals and goals. Nor does he lack intellectual stimulation, for he is constantly confronted with all of the newest and many of the oldest drug problems in medicine. Few physicians are privileged to enjoy the great breadth of personal contacts with outstanding investigators and leading medical authorities that routinely befalls the Food and Drug Administration physician. In fact, few physicians are privileged to shoulder the responsibility for the safety and integrity of our nation's drugs.

The work of the Food and Drug physician is diversified in character and content. The horizon of the work extends from new to old drugs, from antibiotics to analgesics, from electrotherapy to electro-quackery, from labels to literature, and from records to research. The establishment of clinical studies in support of court cases and the recruiting of expert medical testimony is a major medical activity. The physician is called upon to work with staff members representing all other functions of the Administration. This provides opportunity for the physician to use his specialized professional training and knowledge and integrate himself into the over-all program of the Food and Drug Administration.

The American pharmaceutical industry is the finest and most progressive in the entire recorded history of the world. As a result of its vigor, a tremendous, challenging task is imposed on the medical staff of the Food and Drug Administration. The work of the physician in the New Drug Branch is perhaps the most demanding and taxing of any in government. The review and analysis of original investigative data present, in themselves, many unique problems. Often it is useless to refer to the standard textbooks of pharmacology, for the information at hand on a new drug is that which will appear in the texts two or more years hence. The translation of animal data and interpretation of the necessarily limited human studies with a new drug impose great responsibility on the physician. He must clearly reach a decision that may affect many lives. The law further requires that such decision be reached within 60 days. This is a short enough time when one considers the complexity of the problems of new drugs and experimental therapeutics.

The physician in the Food and Drug Administration has many satisfying avenues of professional endeavor open to him. His daily decisions affect more people—more patients—than he could otherwise see professionally in a year. The Food and Drug physician rightfully can take pride in his service to his fellow physicians and to his patients—the American public.

GENERAL PRACTICE CLINICS

This section of General Practice Clinics features reports of papers delivered at current medical meetings in the United States and abroad.

Antibiotic Therapy of Bacterial Infections of the Skin

Presented by LAWRENCE KATZENSTEIN, M.D., (Delaware, Memorial, and Wilmington General Hospitals) before the Medical Society of Delaware, Wilmington, October 17 to 18, 1955.

In the treatment of skin infections, two groups exist: a primary infection group, such as impetigo, and secondary infections, such as stasis dermatitis or otitis externa. Most bacterial infections of the skin contain *Staphylococcus aureus*. The author mentioned only the pyodermas. He believed that topical penicillin was contraindicated due to the development of sensitivity. Bacitracin and neomycin were preferred, since they are practically never used systemically. Antibiotic ointment was most effective in the treatment of small areas of involvement. Treatment should continue for one week after the inflammation has subsided. Cortisone may also be used to reduce the inflammation if the eruption is severe and widespread.

Contraindications to the use of ointments were: (1) acute weeping exzematous eruptions; (2) pyodermas of the scalp in females; (3) intertrigo; (4) furuncles and carbuncles. The author believed it was usually advisable to use systemic therapy in these situations. He preferred oral penicillin; 41 out of 47 cases so treated cleared in one week. Of the remaining 6, 5 showed a resistant organism. Twenty-six per cent of the outpatients treated in the clinic showed resistance to penicillin, as versus 75 per cent of the patients in the hospital. This was due to the fact that hospital personnel were carriers of resistant staphylococci. Penicillin was better than broad-spectrum antibiotics, especially since fungus infections were likely to occur with the use of the latter. Systemic intramuscular penicillin was not indicated in pyodermas, since anaphylactic shock might be caused.

The Use of a Steroid Anesthetic Agent

Presented by FRANK J. MURPHY, M.D., AND NERI P. GUADAGNI, M.D., (Department of Anesthesiology, University of California Medical Center) before the American Society of Anesthesiologists, Boston, Mass., October 20 to November 2, 1955.

This report is a follow-up on the clinical use of 21-hydroxypregnanedione sodium succinate. This drug has anesthetic value and produces very few side reactions. At the University of California, it was found that it did not interfere with oxygen metabolism in the brain. It was first used as an anesthetic agent in humans for a prefrontal lobotomy, with good success. It was then used very carefully by the

author in good risk patients and found to be a very good basal anesthetic. When used with nitrous oxide and oxygen in a 3:1 mixture, a very satisfactory surgical state of anesthesia was produced.

Relaxant drugs may be added, or, for deeper narcosis, various other drugs may be used with it, such as barbiturates, ether, or cyclopropane. The advantages of 21-hydroxypregnanedione sodium succinate are: (1); it is a satisfactory basal anesthesia; (2) it may be used for long periods of time (nine hours is the longest the drug has been used to date); (3) it can be used in all age groups (9 years to 80 years by the author to date); (4) it is an innocuous drug. It has been used in very poor risk patients. The author has used the drug on patients whom he considered too poor a risk for any anesthesia.

The one undesirable feature of the drug is the high incidence of thrombophlebitis which has been associated with its use. The author had three cases of this in his early experience with the drug, and it has been reported frequently by other workers. It was first used in a buffered solution, but this did not decrease thrombophlebitis. The author has found that by getting the drug into the circulation as rapidly as possible, he has completely solved the problem. Intravenous injection is started through an 18 gauge needle with a good flow; a 2.5 per cent solution of the drug in water is injected rapidly into the tubing. The adult dose of the drug is 0.5 to 2.0 Gm. administered in two to four minutes. After 10 minutes, the patient may be intubated or other drugs started.

A Study in Controlled Therapy of Degenerative Arthritis

Presented by EUGENE F. TRAUT, M.D., and EDWIN W. PASSARELLI, M.D. (Chicago), before the American Rheumatism Association, Atlantic City, June 3 and 4, 1955.

The various forms of chronic arthritis have a fluctuating natural history characterized by remission, relapses, and progression. The importance of the psyche in the pathogenesis and course of arthritis is increasingly apparent. On these accounts and to satisfy the natural desire of the patient to initiate treatment at his first visit, we decided to fashion a base line by placebo therapy. Besides serving as a control on the effects of other measures, placebos would not interfere with such laboratory procedures as measurement of the uric acid level in the serum, the sedimentation rate of erythrocytes, or the various serologic tests. The placebo procedures instituted were lactose tablets and subcutaneous injections of saline. The tablets were exhibited first. If the patient failed to be improved by tablet placebo, or initially was benefited only to fail to improve later; the injection placebo was instituted. The patients were interviewed and examined as to their progress by six rheumatologists, each being careful to maintain a casual, nonsuggestible attitude. The effects were volunteered by the patients and obtained by inquiry and by physical as well as laboratory examination. Data were assembled on various forms and were broken down according to the race and sex of the patients.

Over 182 patients with degenerative arthritis were studied in this manner for one and a half years. More than half of the patients receiving lactose tablets experienced

relief, justifying continued visits to the clinic and the abandoning of previously used salicylates and proprietaries. Those initially unresponsive to tablets and those eventually ceasing to improve on tablets were treated by subcutaneous injections of normal saline solution. Approximately the same percentage of those patients not helped by tablet medication responded favorably to the salt water injections. There was a sex and race difference in placebo response. Difference in severity of joint involvement also affected the response to placebos. Thus, the combined tablet and injection procedures satisfactorily helped significantly 75 per cent of the patients with degenerative arthritis.

The conclusion is drawn that such a controlled placebo study is necessary in determining the fitness of newly proposed treatments to enter our already too thick pharmacopeias and books on therapy.

Advanced Mammary Cancer

Presented by GORDON W. BETHUNE, before the International College of Surgeons, Philadelphia, September 12 to 15, 1955.

It is known that some breast cancers will respond to therapy with various hormones. Recently, studies have been done using hypophysectomy in the treatment of breast cancer. The functions of the target glands should be decreased if the secretions of the pituitary are removed. The author presented studies done on patients with inoperable breast cancer. The survey was done in these patients for palliation and as an experimental measure.

One patient had severe back pain; two weeks after hypophysectomy, the metastases in the axilla disappeared and the bone pain was gone. The primary lesion was a large breast cancer. The local lesion itself was almost gone in four months. The disease continues to remain arrested after 20 months. The metastatic bone lesions are completely filled in.

In the second patient, there was no appreciable improvement. The third patient obtained almost complete relief of pain, but little change in the metastasis. The fourth patient had no relief of pain or change in the size of the lesion. The fifth patient had a bilateral ovariectomy for metastatic cancer with no effect. However, she obtained complete relief from the pain following a hypophysectomy. Nine months after her operation the pain has not recurred and she appears quite well. In the sixth patient, a woman of 52, back pain had been present since 1954. She was operated on in January, 1955, and has had complete relief from pain up to the time of this report.

The author has noted that the site of the secondary lesion may be of some importance. The outlook seems to be better when the metastatic spread is to bone only. Estrogen excretions in the hypophysectomized patients were within normal limits in 2 patients with good results. They were below normal limits in several patients with poor results. It, therefore, seems that other factors must be considered. The excretion of follicle-stimulating hormone was decreased in all cases. There was no postoperative mortality.

Preliminary Clinical Experience with Metacortandracin in Rheumatoid Arthritis

Presented by EDWARD W. BOLAND (Los Angeles), before the American Rheumatism Association, Atlantic City, June 3 and 4, 1955.

Clinical observations on the effects of metacortandracin (Δ^1-dehydrocortisone) in 52 patients with active peripheral rheumatoid arthritis, treated uninterruptedly for periods of three to five months, are summarized. The study, which is still in progress, was designed to determine: (1) the effects of the compound when given as initial therapy; (2) dosage schemes for its practical application; (3) the relative antirheumatic potencies of metacortandracin and hydrocortisone; and (4) the therapeutic efficiency of metacortandracin as compared to that of hydrocortisone on continued administration.

Group 1. The response to metacortandracin employed as initial therapy was observed in 11 patients. Suppressive doses were varied with the severity of the disease and ranged from 15 to 30 mg. a day. Prompt and striking antirheumatic effects resulted in 10 of 11 patients, the pattern of improvement being similar to that noted with hydrocortisone and cortisone given in larger suppressive amounts. Subjective relief began within 3 to 72 hours following the first divided dose, and objective improvement was noted within two to seven days. With the dosages employed, adequate suppression of the disease was achieved in 9 patients after 7 to 21 days of administration. With daily maintenance dosages ranging from 7.5 to 25 mg., major improvement was upheld for three to five months in 9 of the 11 patients. One or more adverse signs appeared in 7 patients, these being minor in 5, but sufficient in 2 to cause limitation of dosage below optimally effective levels.

Group 2. Estimates were made of differences in antirheumatic potency between metacortandracin and hydrocortisone in 14 patients. This was accomplished by transferring treatment directly to the new compound in patients whose disease was adequately, but not completely, controlled on established and quite stable maintenance amounts of hydrocortisone. In each instance, the dosage of metacortandracin required to maintain approximately an equivalent degree of improvement was smaller. Dosage ratios of metacortandracin to hydrocortisone varied from 2.4:1 to 5.3:1, and averaged 3.97:1. Later the dosage of metacortandracin was increased above equivalently effective amounts, and in 13 of the 14 patients, greater benefits were provided and maintained.

Group 3. In 27 patients whose clinical control was unsatisfactory while being maintained on hydrocortisone, treatment was transferred to metacortandracin. In 25, the immediate results were favorable; major improvement was achieved or restored following the institution of smaller, but more effective, doses of the new steroid.

After three to five months of continuous metacortandracin therapy, 16 of the 27 patients (59 per cent) were classified as adequately improved. In general, the percentage of patients demonstrating satisfactory control depreciated as the treatment was prolonged: improvement was considered as adequate in 74 per cent after one month, in 89 per cent after two months, in 78 per cent after three months, in 58 per

cent after four months, and in 50 per cent after five months. Nine patients responded well at the beginning, but their results deteriorated later because responsiveness to the drug diminished and because side effects intervened or became more pronounced, and to a degree that, with respect for prudency, prohibited further increases in dosage. At analysis, the dosages of metacortandracin varied from 7.5 to 30 mg. a day, and averaged 16.7 mg. for the group.

Twenty-four patients exhibited one or more hormonal complications when the transfer from hydrocortisone was made. A total of 87 individual effects was noted. After three to five months of metacortandracin administration, all 27 patients displayed unwanted reactions, and a total of 94 separate effects was recorded. Twenty-seven side effects disappeared, eight lessened in degree, 24 remained unchanged, and 28 became more pronounced. Thirty-four "new" signs developed during administration of the new analogue, many of which were gradually cumulative and increased as the treatment period lengthened. Although most of the reactions were mild or moderate in severity, they were, alone or in combination, troublesome enough in 10 patients to limit dosage and prevent the maintenance of satisfactory results.

Conclusions Drawn. Short-term observations indicate that metacortandracin has certain advantages over hydrocortisone in the treatment of rheumatoid arthritis. These consist mainly in its lack of salt and water retention with ordinary therapeutic doses, its capacity to restore adequate improvement in patients who have lost satisfactory control after prolonged hydrocortisone administration, and its ability to maintain the greater benefits in a significant percentage of such patients for periods up to five months, at least. However, the other difficulties and potential hazards encountered with the older steroids seem to be shared by the new derivative. Indeed, some adverse reactions, notably digestive complications, ecchymotic skin lesions, and vasomotor symptoms, have occurred more frequently and have been more troublesome with the new analogue. Thus, metacortandracin is far from an ideal suppressive agent for rheumatoid arthritis. However, it possesses some important refinements, and to us its discovery strengthens the conviction that, through further permutations of chemical structure, steroids with higher therapeutic efficiency may be developed in the future.

Arthritis in the Elderly Patient

Presented by JOSEPH J. BUNIM (National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland) before the 28th Graduate Fortnight of the New York Academy of Medicine, October 11, 1955.

Osteoarthritis may be due to either or both of the following causes: (1) primary osteoarthritis due to senescent aging of cartilage; (2) secondary osteoarthritis, occuring secondary to mechanical injury of articular hyaline cartilage, such as in excessive weight bearing or excessive motion. When osteoarthritis occurs in the distal interphalangeal joints, it is called Heberden's nodes. Osteoarthritis is the most common type of arthritis. It is the second most common musculoskeletal disease.

Bursitis is the most common musculoskeletal disorder. Osteoarthritis is much more frequent than rheumatoid arthritis and gout.

The joints affected in osteoarthritis are: spine, 73 per cent; knees, 25 per cent; hips, 7 per cent; other joints, 5 per cent. The sequence of pathologic events in osteoarthritis is as follows. (1) Degeneration of articular cartilage: there are changes in the cellular constituents and a change in the interfibrillary strands in the cartilage from fine to coarse strands. The matrix loses water, becomes hard and less elastic. There are alterations in the collagen tissue. (2) Productive changes secondary to destructive changes: calcification of cartilage and changes in the subchondral bone occur; blood vessels and fibroblasts proliferate and cause the formation of new bone. This process is called eburnation. The marrow spaces of the new bone communicate with the marrow spaces of the epiphyses. There are also changes in the synovial lining of the joint. With the onset of these changes there is thickening, tightening, and pain in the joints. Multiple bone cysts form which communicate with the joint space; it is thought that these cysts form secondary to an increase in intraarticular pressure. All these changes lead to displacement of bone and to joint dislocation.

There is a possible relation between osteoarthritis and the endocrine glands since there is an increased incidence of osteoarthritis in patients with acromegaly and with obesity. It was found that the anterior pituitary hormone caused an increase in the growth of articular cartilage and the degeneration of ground substance and caused the development of degenerative joint disease in mice. The treatment of osteoarthritis includes rest, aspirin, physiotherapy, weight reduction, tertiary butyl acetate of hydrocortisone given intra-articularly, and surgery (only in a small percentage of cases), such as arthrodesis, arthroplasty, and debridement.

The Use of Fructose in Treatment of Diabetic Acidosis

Presented by MAX MILLER, before the Connecticut State Medical Society, New Haven, September 14 and 15, 1955.

The author reviewed the modern treatment of diabetic acidosis which includes (1) insulin, (2) water, (3) sodium, (4) potassium, (5) plasma expanders, (6) alkali (?), and (7) carbohydrate (?). He noted that when glucose is used initially in treatment there is a greater utilization of glucose, but this is accompanied by increased glycosuria and urine output. The use of fructose intravenously results in an even greater utilization of carbohydrate without significantly increasing water, sodium, or potassium excretion in the urine. Fructokinase apparently does not require insulin for its action, as does glucokinase, and this is especially helpful in the initial stages of treatment of diabetic acidosis when insulin resistance is often a factor. By catheterization studies in humans, it was shown that fructose given intravenously is removed by the liver twice as rapidly as glucose, and this more rapid removal is unaltered in diabetic acidosis. Isotope studies indicated no impairment of oxidation of fructose to carbon dioxide in the diabetic state, even in the absence of insulin.

BOOK REVIEWS

Causal Factors in Cancer of the Lung. Carl V. Weller. Springfield, Ill., Charles C Thomas, 1956. 11 pp. $3.00.

Cancer of the lung is at present in the front rank of medical controversy, particularly in the field of etiology. Dr. Weller's timely monograph will satisfy none of the extremists, being a sober and factual account of the various factors that may enter into bronchogenic carcinoma. The author points out that in view of the alarming increase in the incidence of lung cancer in recent decades, it is most likely that causal factors should be sought in environmental changes. Certain modern industrial operations are suspected of increasing the danger of pulmonary cancer in occupational groups, such as workers in tar, chromate, and asbestos plants. The increase in air pollution, particularly with hydrocarbons from motor vehicle exhausts, must also be viewed with suspicion, although no direct causal relationship has yet been proved in man.

A whole chapter of the monograph is devoted to the currently debated topic of a possible association between smoking tobacco and lung cancer. A résumé is presented of the various statistical studies made here and in England, though no mention is made of Dr. Joseph Berkson's trenchant and deflatory analysis of these statistical data,* possibly because time did not permit its inclusion. Even so, the monograph is a useful and practical guide to all those interested in one of the "hottest" medical topics of the day.

Cancer of the Lung. Pathology, Diagnosis and Treatment. Milton B. Rosenblatt and James R. Lisa, with Chevalier L. Jackson, George N. Papanicolaou, N. Chandler Foot, J. Maxwell Chamberlain, Charles F. Daniels, and Bernard Roswit. New York, Oxford University Press, 1956. 330 pp. illus. $15.00.

Cancer of the lung has become the major problem in the field of pulmonary diseases, with a continued rise in incidence in the United States and most European countries. This book is therefore a most timely and valuable contribution to an understanding of this complex and often baffling clinical entity. Baffling because, as the authors point out, the hope that improved methods of diagnosis introduced in recent years would help to recognize early cases has not been realized. Diagnosis is made no easier by the ability of bronchogenic carcinoma to masquerade as pneumonitis, tuberculosis, bronchiectasis, and a variety of other pulmonary disorders. The indifference of patients to their early symptoms, and the failure of some physicians to include cancer of the lung in their differential diagnosis, both contribute to the present alarming state of affairs.

This exceptionally well designed volume, profusely and excellently illustrated, should go far to bring clinicians and general practitioners up to date with the prob-

*Berkson, J.: Proc. Staff Meet., Mayo Clin. 30:319 (July 27) 1955.

lem. The pathology of the disease is thoroughly explored, including the various avenues of spread of tumors. The chapter on clinical manifestations is thoroughly documented with case illustrations, as is the chapter on physical diagnosis. The extensive section dealing with roentgen examination comprises a large number of well reproduced roentgenograms. Dr. Jackson contributes a special section on bronchoscopy, while the chapter on exfoliative cytology by that pioneer of cytologic diagnosis, Dr. Papanicolaou, and Dr. Foot serves as a handy introduction to this modern technique. In the section on the treatment of tumors, Drs. Chamberlain and Daniels review the surgical measures available, while Dr. Roswit discusses palliative treatment of the disease, including roentgen therapy, nitrogen mustard drugs, and the latest radioisotope techniques. All chapters are extensively documented with bibliographies.

Drs. Rosenblatt and Lisa, the principal authors and editors, are to be warmly congratulated on producing this outstanding work which ranks with the best textbooks of its kind. The writing is lucid, the case histories aptly chosen, the tabular and graphic data are clear, and all vital points are suitably illustrated. The book cannot be too strongly recommended for the medical bookshelf.

Tratamiento de la Meningitis Tuberculosa y de la Tuberculosis Pulmonar Aguda (Treatment of Tuberculous Meningitis and Acute Pulmonary Tuberculosis). Juan Torres Gost, M.D., Madrid, Espasa Calpe, S. A., 1955. 122 pp. (illus.), in Spanish.

This excellent monograph on meningitis and tuberculosis is the result of the author's long experience with these two disease entities in Spanish hospital and health services. It covers both subjects precisely and authoritatively, with numerous illustrations, case histories, and clinical charts.

The treatment of tuberculous meningitis favored by the author is with streptomycin and isoniazid, with the complementary use of PAS and Conteben (*p*-acetylaminobenzaldehyde thiosemicarbazone). In acute tuberculosis, he favors streptomycin and isoniazid, also with the complementary use of PAS and Conteben.

An interesting chapter contains the author's thoughts on the social implications of tuberculosis. All the organs of the state and of the medical services must be coordinated to educate the public and to overcome certain age-old prejudices. The extension of radiographic examination services is one primary requisite for early detection of tuberculous processes. In all, the author believes that the treatment of tuberculosis has entered a new era.

The style of the book is clear and can easily be read by anyone with a passing knowledge of medical Spanish, and we highly recommend its reading.

The Dispensatory of the United States of America. 25th Edition. Philadelphia, J. B. Lippincott Co. 2139 pp. $25.00.

Since the publication of the last edition of this indispensable work in 1947, minor revolutions have occurred in some fields of chemotherapy, requiring extensive revision. Thus there are now new general survey articles on such agents as adrenergic

blocking drugs, anticoagulants, antihistamines, antimetabolites, curarimimetic agents and their antagonists, ganglionic blocking agents, cholinesterase inhibitors, etc. The survey on antibiotics has, of course, had to be entirely rewritten to include the newest broad-spectrum agents. The total of new admissions to the *United States Pharmacopeia*, the *National Formulary*, the *British Pharmacopoeia*, and the *New and Nonofficial Remedies* list since 1947 exceeds 500 items. The new information for this edition was chosen from more than 25,000 issues of approximately 400 medical, pharmaceutic, biologic, and chemical journals used by the editors for their revision, a truly remarkable feat of research and editing.

Among the new drugs or substances amply documented are ACTH, cortisone and its derivatives, Rauwolfia compounds, chlorpromazine, and radioisotopes. Penicillin in 137 varieties is described in 28 pages. Among the items that have been quietly dropped from this edition are about 500 items, most of them herbal remedies. These include cypripedium (lady's slipper), once popular as a sedative in hysteria and neuralgia, and diabetes weed. The quaintly named "quack grass" (Triticum) has been retained, although some faint doubt is thrown on its alleged efficacy in urinary tract disorders.

The volume is divided into four parts. The first provides a complete commentary on the drugs recognized by the U.S., British, and International pharmacopeias, and the National Formulary X. The second part lists the nonofficial drugs, also certain formerly official drugs and various chemical substances of toxicologic interest. Part Three covers drugs in veterinary usage, while Part Four is the exceptionally thorough functional index of 80 pages. The editors, contributors, and publishers are to be congratulated for producing an outstanding work that does great credit to the Dispensatory's 122 years of history.

To be published

In the April issue of the INTERNATIONAL RECORD OF MEDICINE

SYMPOSIUM ON THE TRANQUILIZING AGENTS IN CLINICAL MEDICINE

■ Howard D. Fabing	The New Pharmacologic Attack in Psychiatry
■ F. M. Berger	Meprobamate: Its Pharmacologic Properties and Clinical Uses
■ Frank J. Bonello	Chlorpromazine in General Practice
■ Frank J. Vinci and J. Campbell Howard, Jr.	Use of the Tranquilizing Properties of Reserpine
■ Thomas G. Allin, Jr., and Raymond C. Pogge	Azacyclonol and Pipradrol in General Practice

Also to be included in the April issue are the following: "The Medico-Pharmaceutical Arts of 'La Celestina'" by Félix Martí-Ibáñez; International Clinical Newsletter; and the section General Practice Clinics, which presents advanced reports of medical meetings and abstracts of current medical literature.

Kalinga Prize Awarded to Dr. Augusto Pi-Suñer

Dr. Augusto Pi-Suñer, former Professor of Physiology at the University of Barcelona, Spain, and presently Professor Emeritus of the National University of Venezuela in Caracas, has been awarded the Kalinga Prize by the United Nations Educational, Scientific and Cultural Organization.

UNESCO

Dr. Augusto Pi-Suñer

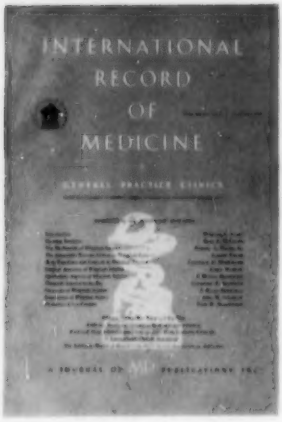
The prize of £1,000 ($2,800) was established by UNESCO in 1952 to give recognition to the achievements of writers on science, particularly in the interpretation of science and research for the public.

Dr. Pi-Suñer was born in Barcelona, Spain, in 1879 and obtained his doctor's degree from the University of Madrid. He was later distinguished for his outstanding work in Physiology, with degrees of Doctor Honoris Causa from the universities of Coimbra (Portugal), Toulouse (France), Caracas (Venezuela), and Montevideo (Uruguay). He was President of the Academy of Medicine of Barcelona for a number of years. At the end of the Spanish Civil War he moved to Venezuela where he organized the Institute of Experimental Medicine at the National University and directed it until his retirement. He is a member of many academies and medical societies in Spain, France, Argentina, Venezuela, Germany, Mexico, and the United States, and the author of many books, among them the book *Sistema Neurovegetativo*, the most important publication on the subject in our time.

His long list of publications includes several books: *Fisiología General* (1909); *La Unidad Funcional* (1917); *Los Mecanismos de Correlación Fisiológica* (1920); *La Sensibilidad Trófica* (1941). In the field of popular interpretation of science, he is the author of *Principio y Término de la Biología* (1941) and *Clásicos de la Biología* (1942) later published in English as *The Bridge of Life* (Macmillan Co., New York, 1951) and *Classics of Biology* (Pitman & Sons, Ltd., London, 1955). His book *Sistema Neurovegetativo*, published in Mexico (first edition, 1947; second edition, 1954), was honored with the Prix Pourat of the Academie des Sciences de Paris and the Institut de France, as the most significant scientific book to appear during the year.

Dr. Pi-Suñer is a member of the International Editorial Board of the INTERNATIONAL RECORD OF MEDICINE & GENERAL PRACTICE CLINICS.

outstanding part of the history of medicine . . .



1837

When the AMERICAN MEDICAL INTELLIGENCER was founded in 1837, Victoria had just become queen, Andrew Jackson had finished his second term as President, and Pasteur, Virchow and Lister were all three schoolboys. The INTELLIGENCER not only published the most up-to-date medical news of the time but also waged untiring war on quacks and cure-all nostrums.

1956

Today, its direct descendant is the INTERNATIONAL RECORD OF MEDICINE AND GENERAL PRACTICE CLINICS, carrying on the tradition of keeping the medical profession abreast of the most modern methods of treatment. It contains original papers by leading medical authorities, clinical data and advance reports on current medical meetings. A special feature is the *symposia* on vital medical topics of the day such as the new technique of artificial hibernation, motion sickness, broad-spectrum antibiotic therapy, the art of medical writing, atomic medicine, endocrinology and psychiatry. The journal is unique in its scholarly approach to the medical humanities, correlating medicine with history and the fine arts. Félix Martí-Ibáñez, M. D., is the Editor.

Among its many eminent contributors: Selman A. Waksman,* E. B. Chain,* Hans Selye, Henry Sigerist, Douglas Guthrie, Wallace Herrell, Henri Laborit, Henry Welch, Walter Alvarez, and Hugh Cleghorn.

* *Nobel prize winner.*

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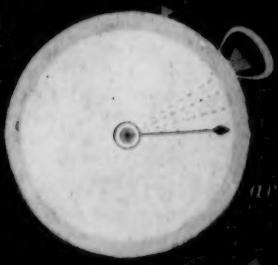

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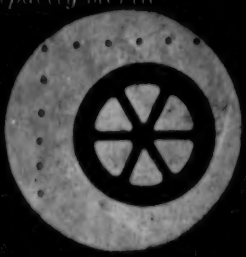

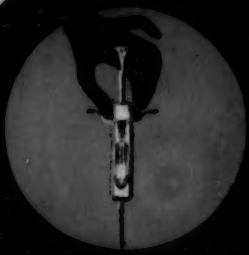

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